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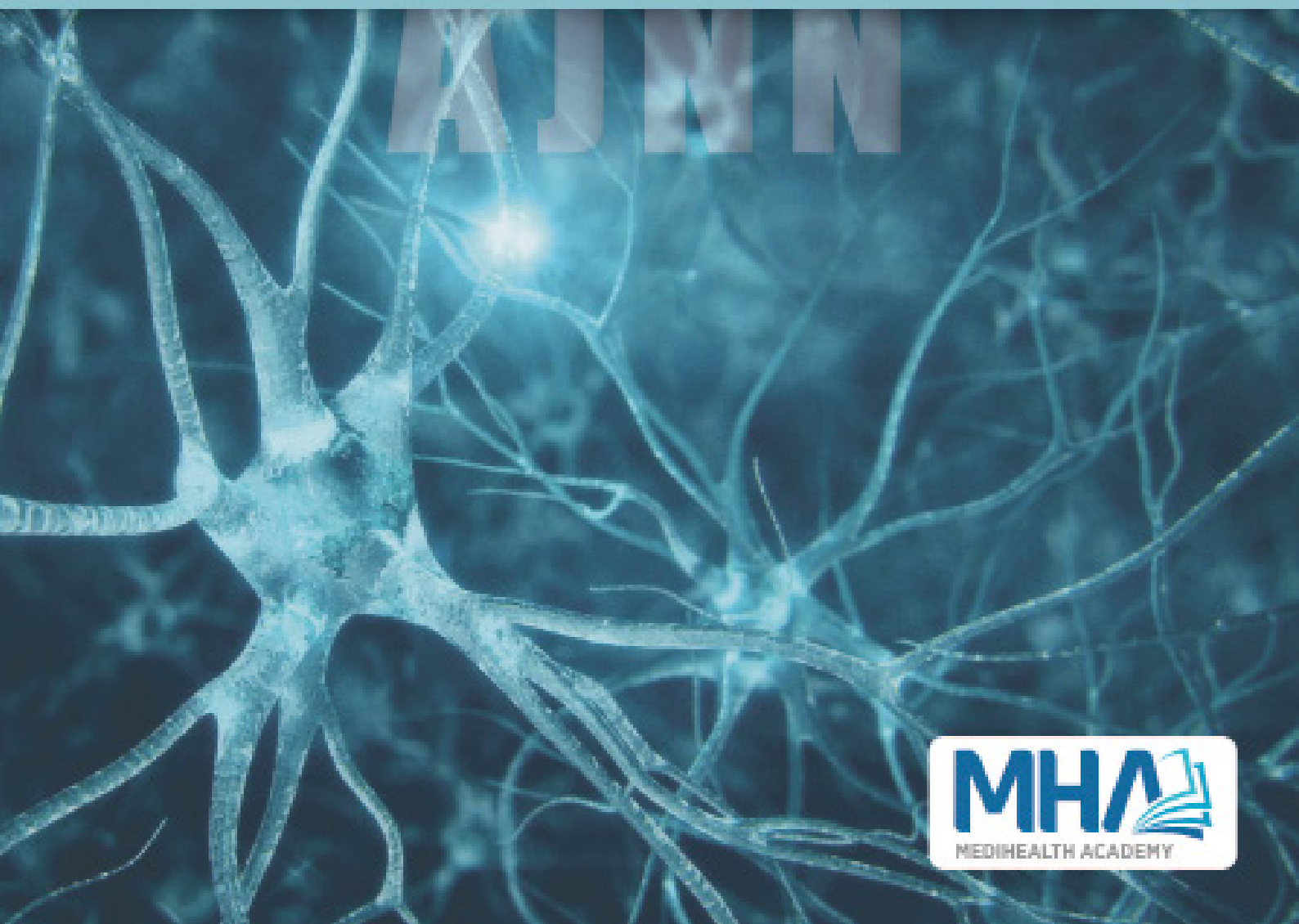

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Entrapment neuropathies of the upper extremity

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ABSTRACT

Entrapment neuropathies are mononeuropathies caused by long term or recurrent compression of peripheral nerves as they pass through anatomically narrow areas. The diagnosis of entrapment neuropathies are based on a combination of anamnesis, physical examination and EMG findings. In this article, pathophysiology of entrapment neuropathies and some of the most common entrapment neuropathies seen in upper extremity will be discussed.

Keywords: Entrapment neuropathy, mononeuropathy, neuropathy, carpal tunnel syndrome upper extremity

INTRODUCTION

Entrapment neuropathies are mononeuropathies caused by long term or recurrent compression of peripheral nerves as they pass through anatomically narrow areas. Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy in clinical practice which is followed by cubital tunnel syndrome (CuTS).[1] Tarsal tunnel syndrome and radial neuropathy are other common conditions.[2,3] Syptoms may vary from pain, sensory deficit, paresthesia to muscle atrophy and permanent motor deficit depending on the degree of damage.[4] Early identification is crucial in determining the treatment approach and preventing damage progression.[2-4]

Commonly used synonymously in daily practice, entrapment neuropathy and compression neuropathy are different entities. Compression neuropathy refers to any damage to the nerve caused by acute or chronic compression. Entrapment neuropathy refers to damage caused by mild, long-term or recurrent compression. Some anatomical factors increase the risk of entrapment. These are localization and being adjacent to structures that may facilitate compression.[5,6]

Entrapment neuropathy is a very common condition in society. For example, the lifetime prevalence of carpal tunnel syndrome is 10% and this rate reaches 84% in patients with type 1 diabetes. It is twice as common in women than in men. Age distribution is bimodal, peaking between 25-30 years (related to occupation) and 40-60 years (because of hormonal factors). Pregnancy; various connective tissue diseases, (especially rheumatoid arthritis) endocrinological disorders; obesity or rapid weight loss; presence of polyneuropathy in the background; edema; presence of amyloidosis are some of the conditions that increase the incidence.[1,3,6-9]

In this article, pathophysiology of entrapment neuropathies and some of the most common entrapment neuropathies seen in upper extremity will be discussed. Shoulder girdle entrapment neuropathies are excluded due to the breadth of the topic.

PATHOPHYSIOLOGY

In entrapment neuropathies, there is a long-lasting or frequently recurring micro trauma of mild severity and nerve damage due to this trauma.

Intraneural transient ischemia is the first sign of entrapment. External compression of the nerve with a pressure above 20-30 mmHg is sufficient to disrupt venous circulation in the vasa nervorum. The pressure gradient must be normalized intermittently to ensure adequate blood flow to the area. Therefore, at this stage, paresthesia occurs which is triggered at night, in static position or in extreme positions and disappear with movement.[1]

Prolonged ischemia damages the vasculature followed by edema. The entrapped nerve may be visualized as enlarged and hyperintense on MRI.[7] Continuation of edema initiates both extraneural and intraneural fibrotic changes.[1]

The inevitable result of prolonged ischemia is focal demyelination which is characterized by segmental slowing of conduction velocities or, if damage developed acutely, conduction blocks.[8]

Structural changes occur in Ranvier nodes with demyelination. These changes lead to the generation of spontaneous ectopic action potentials. This is reflected in the clinical practice as a sudden electric-like pain, which may occur spontaneously or be triggered by Tinel test. Eventually, if the compression persists, permanent axonal damage occurs through Wallerian degeneration.[1,6,9,10]

Inflammation is known to play a role in nerve damage. Immune cells are activated at the damaged axonal site and release inflammatory cytokines. This increases damage to the vasculature and initiates a cycle of further inflammation and edema. Furthermore, mechanical compression and inflammation inhibit retrograde and anterograde transport in the surrounding axons. All metabolites that cannot be transported cluster in a restricted area and mediate the formation of new ion channels. This contributes to sensitization at the site of compression.[1,11-14]

CLINICAL FINDINGS

The diagnosis of entrapment neuropathies are based on a combination of anamnesis, physical examination and EMG findings. EMG is used not only to support the diagnosis but also to exclude alternative diagnoses; determine the exact location of the compression, predict the prognosis and to select the optimal treatment strategy.[6,15-18]

Typical EMG findings are focal slowing (prolonged latency, decreased conduction velocity). Since axonal damage does not occur immediately, there is no initial loss of amplitude and needle EMG shows no abnormal findings. Focal demyelination begins after 7-10 days of exposure, followed by remyelination on days 14-28. The disruption of the saltatory conduction via demyelinated areas and remyelinated fibers being thinner than normal prolong the time between stimulation and action potential generation.[1-4,19-24]

As the process goes on, first sensory and then motor amplitude decrease. Increased input activity, fibrillation, PSW (positive sharp waves) and large MUAPs (motor unit action potentials) can be observed on needle EMG. Amplitude loss is an important indicator of the severe damage.[4,6,10,15,26]

When evaluating EMG results, it is important to note whether there are any anastomoses between the nerves.[8,13,27,28] The most common one is the Martin Gruber between the median and ulnar nerves in the forearm. Here, some fibers of the median nerve or anterior interosseous nerve are carried over the ulnar nerve and innervate the intrinsic muscles of the hand.

There are three signs of this on EMG: initial positive deflection of the CMAP (Combined Muscle Action Potential) when the median nerve is stimulated at the wrist and the electrodes are placed over the abductor pollicis brevis; increased or negative median nerve conduction velocity (because some fibers do not pass through the carpel tunnel); larger CMAP amplitude on proximal than distal (because some of the distal fibers are carried through the ulnar nerve.[33,34]

Abnormalities that may compress the nerve can be scanned via MRI (magnetic resonance imaging). Findings indicating nerve damage can be revealed. Additionally, denervated muscles can be demonstrated.[15,19]

In USG, a normal nerve has a "honeycomb" appearance with groups of hypoechoic fascicles surrounded by hyperechoic perineurium. Also the nerve itself is surrounded by hyperechoic epineurium, which often blends indistinguishably into the surrounding tissue. In entrapment neuropathy, venous congestion causes widening of the cross-sectional area of the nerve, while ischemia causes flattening of the nerve and disruption of the normal fascicular structure. This widening may also be shown proximal to the entrapment due to impaired axonal transport.[18-20]

Increased vascularity due to inflammation and perineural fibrosis may be demonstrated on USG as echogenic halo appearance (thickening and prominence of the epineurium), intraneural echogenic fibrotic spots and pseudo neuroma formation. "Hourglass appearance" develops as a result of flattening of the nerve. USG also reveals hyper echogenicity in denervated muscle due to edema in the acute phase and increased heterogeneity, structural disruption and replacement of normal muscle tissue with fatty tissue due to atrophy in the chronic phase.[15,19]

MEDIAN NERVE

The median nerve is formed by the merger of fibers from the medial cord (C8-T1) and lateral cord (C5-C7) of the brachial plexus. It runs parallel to the brachial artery and ulnar nerve in the sulcus bicipitalis. It does not branch until the elbow level.[16]

When it reaches the antecubital fossa, it passes between the two heads of the pronotor teres (PT) after innervating the forearm flexor muscles palmaris longus (PL), flexor carpi radialis (FCR), PT, flexor digitorum superficialis (FDS). Here it crosses the ulnar artery anteriorly and gives the anterior interosseous nerve (AIN) branch. The AIN runs deep within the fibrous margin of the FDS. It innervates the flexor pollicis longus (FPL), the lateral side of the flexor digitorum profundus (FDP) and the pronotor quadratus.[16-19]

The median nerve extends to the wrist between the FDP and FDS. At the wrist, before passing through the carpal tunnel, it gives off its palmar cutaneous branch innervating the tenar eminence. Then it passes through the tunnel and innervates the thenar muscles and provides sensory innervation to the palmar surface of the first 3.5 fingers.[3,16,23]

The median nerve can be compressed in three places: elbow, forearm and carpal tunnel. In addition, a rare accessory fibrous band, the Struthers Ligament, lies proximal to the elbow between the supracondylar process of the humerus and

the medial epicondyle and can compress both the median nerve and the adjacent brachial artery. This condition is called Struthers syndrome.[3,16,19,21]

Carpal tunnel syndrome is the most common entrapment neuropathy in adults. The mechanism of its occurrence is not completely understood. However, it is suggested that excessive consecutive movements causing microtrauma in the wrist and the presence of osteoarthritis on the background of a nonspecific tenosynovitis facilitate the emergence of the syptoms. It is usually bilateral, predominantly in the dominant hand. Sensory complaints start first. Hypoesthesia and paresthesia are observed in the first three fingers and lateral half of the fourth finger. Thenar eminence is preserved. Patients wake up with numbness in the hand and swelling in the wrist. Complaints are aggravated by positions that require bending or holding the wrist in the air, such as reading the newspaper, driving a car or carrying a bag. After a while, patients experience a numbness that wakes them up at night. Shaking or rubbing the hand significantly relieves the symptoms; this is called the "flick phenomenon". In more advanced stages, motor deficits develop. Impairment in fine skills and weakness in grasping are seen. Thenar atrophy may be present.[2,3]

On examination, when the median nerve is percussed at the wrist level, there may be an electric-like sensation radiating to the fingers. This is called the 'Tinel' sign. Its sensitivity is 30-45% and specificity is around 65%. The Phalen Test is performed by instructing the patient to bend both hands at wrist level, press the backs of the hands together and wait 30-60 seconds. Its sensitivity is around 50-67% but its specificity is only 15-17%.[2]

When performing EMG, the affected extremity should be compared with the unaffected side and the results should be evaluated together with another nerve (mostly ulnar) in the same hand. Fifteen percent of patients may have normal nerve conduction study results even if they experience clinical symptoms. USG may be helpful to evaluate these individuals.

The classification of CTS according to AAEM (American Association of Electrodiagnostic Medicine) is as follows: >0.5 msec difference between median-ulnar nerve peak latencies recorded from the 4th finger is considered mild. Prolongation of the distal latency of the median motor nerve (>4.0 msec) in addition to mild stage symptoms is considered moderate. Decreased motor amplitude with low/absent sensory amplitude is considered severe CTS.[32]

Another areas where the median nerve can be entrapped are between the two heads of the PT, hypertrophic biceps aponeurosis and the proximal part of the FDS. Compression of the nerve between heads of PT is called Pronotor Teres syndrome (PTS), but compression in all other localizations have the same clinical presentation. PTS is usually seen in people who frequently perform pronation and tight grasping movements (carpenters, tennis players, housewives, waiters).[19]

PTS presents itself with pain in the forearm and sensory deficit in the first three fingers and the lateral half of the fourth finger, just like CTS. The main difference between the two is that in PTS, the sensation of the thenar region is also affected due to the involvement of the palmar cutaneous branch. Nocturnal findings are not observed in PTS.[5]

In PTS, complaints are triggered by resistant elbow pronation and flexion of the third finger. However, third finger flexion may also trigger CTS syptoms. Phalen's test is positive in 50% of cases. EMG is usually normal. The anterior interosseous nerve is often entrapped by the tendinous portion of the deep-seated head of the PT. Other less common sites are the proximal end of FDS, Gantzer muscle, accessory head of FDS or FDP. It usually develops after stretching exercises, peripartum period and thrombosis of radial or ulnar artery.[5,19]

Anterior interosseous nerve syndrome (AINS) presents itself with pure motor signs. The patient is unable to make a fist or button a shirt. When the patient is told to hold a piece of paper with the tips of two fingers, they do so by extending their fingers forward instead of curling the two fingers in an "O" shape. EMG shows signs of pure motor deficit. Denervation in the pronotor quadratus, FDP and FPL can be demonstrated via needle EMG.[19]

ULNAR NERVE

The ulnar nerve is the continuation of the medial cord (C8-T1) of brachial plexus after giving fibers to the median nerve. It runs parallel to the median nerve and brachial artery in sulcus bicipitalis for a short time. Shortly after piercing through medial intermuscular septum, it passes under the Struthers arch which connects the medial head of the triceps to the medial intermuscular septum.[19-21]

At the elbow level, it passes posterior to the medial epicondyle, surrounded by Osborne's ligament and the head of the flexor carpi ulnaris (FCU). Here these structures form the cubital tunnel. The medial border of the tunnel is marked by the medial epicondyle and the lateral border by the olecranon. After exiting the tunnel, the nerve innervates the FCU and the ulnar side of the FDP. Ulnar nerve travels between the two heads of the FCU in forearm. It gives dorsal and palmar cutaneous branches before reaching the wrist. At the wrist, it travels together with the ulnar artery in Guyon's canal.[20,21]

The palmar cutaneous branch travels through forearm on the palmar side. At the wrist level, it crosses over Guyon's canal and then innervates the ulnar side of the palm. From a few centimeters proximal to the palmar cutaneous branch, the dorsal cutaneous branch diverges and receives the sensory input of the dorsal ulnar side of the hand, the dorsal 5th finger and the dorsal ulnar half of the 4th finger. After leaving Guyon's canal, the ulnar nerve branches into two parts, the superficial sensory and branch the deep terminal branch. The superficial branch innervates the rest of the ulnar palmar side of the hand, the palmar side of the 5th finger and the palmar ulnar half of the 4th finger. The deep terminal branch is a pure motor branch which innervates almost all of the interstitial muscles of the hand.[21]

The most common sites of ulnar nerve compression are the cubital tunnel and Guyon's canal. Some other areas include Struthers' arc, medial intermuscular septum and between the two heads of the FCU.[19]

Cubital Tunnel Syndrome (CuTS) is the most common entrapment neuropathy of the ulnar nerve. Symptoms include sensory deficit in the medial forearm, hand, 4th and 5th fingers; tenderness in the medial elbow and pain radiating from the elbow to the forearm and hand. Complaints are aggravated at night during sleep or when the elbow is bent. In the chronic period, atrophy occurs in the first dorsal interosseous muscle, intrinsic muscles and hypothenar region. Loss of fine motor skills develop due to intrinsic muscle weakness. The thumb cannot be adducted due to paralysis of adductor pollicis. A claw hand appearance may be observed in which the 4th and 5th fingers are slightly abducted and the metacarpophalangeal joint of the thumb is hyperextended.[19,22]

Narrow cubital tunnel, cubitus valgus deformity, anteriorly located ulnar nerve are factors that increase the risk. The risk is also higher in long-distance drivers, prolonged cell phone users, smokers and those with a history of prolonged compression or trauma to the elbow.[19,22,23]

In examination, the elbow flexion test is performed by flexion o the elbow over 90 degrees, supinating the forearm and extending the wrist. It is considered positive if paresthesia occurs or present paresthesia increases within the first 60 seconds. Tinel's test may be positive when the medial side of the elbow is touched, but this test alone has low diagnostic value as it may be positive in one third of asymptomatic cases. The nerve compression test is performed by applying pressure to the elbow for 10 seconds. It is considered positive if numbness and paresthesia develop. In addition, if the patient is asked to hold a paper between the thumb and index finger, FPL activity becomes evident because the adductor pollicis is not working and the thumb flexes at the interphalangeal joint. This is called Froment's sign.[21]

EMG shows decreased ulnar nerve motor conduction velocity in the elbow segment. It is important to keep the elbow in 70-90° flexion during the measurement for optimal results. When the elbow is flexed, the arcuate ligament elongates and narrows the cubital canal as the ulnar nerve elongates and becomes vulnerable to entrapment. According to the AAEM, EMG findings of cubital tunnel syndrome are as fallows: a an ulnar nerve motor conduction velocity of less than 50 m/sec in the elbow segment with normal forearm and arm findings, an ulnar nerve motor conduction velocity that is .m/sec lower in the elbow than 20% in the CMAP amplitude over the elbow compared to bellow the elbow. Needle EMG shows fibrillation, PSWs and dilution in the participation of motor unit potentials indicating axon loss. These findings are most evident in the first dorsal interosseous muscle.[3,21,24]

Another region where the ulnar nerve is compressed is the wrist, which is more common in cyclists, golfers, basketball players, racquet sports players and in the presence of ulnar artery thrombosis or aneurysm (hypothenar hammer syndrome). Since the nerve divides into deep and superficial branches at the wrist level, findings in this region may be pure motor, pure sensory or mixed. There are no symptoms on the dorsum of the hand because the dorsal cutaneous branch is spared. Entrapment here can occur in four ways: At pisiform bone proximal to Guyon's canal, within the canal (deep motor branch), distal to the canal at the hook of the hamate bone (deep motor branch) and distal to the canal in the palmaris brevis muscle (superficial sensory branch). The compression within the canal is called Guyon's canal syndrome (GCS). In GCS, the sensory deficit involves only palmar side of the 4th and 5th fingers. The dorsum of hand, ulnar side of palm are spared. Furthermore, in CuTS the medial forearm is also affected, whereas in GCS the symptoms are limited to the hand. Apart from these differences, the findings are similar in both conditions. Patients with suspected GCS should be evaluated for hamate, pisiform fractures and vascular pathologies. Demonstration of latency prolongation in the wrist on EMG supports the diagnosis.[5,19,21]

RADIAL NERVE

The radial nerve is the continuation of the posterior cord originated from the C5-T1 roots. It runs posterior to the axillary artery. Then, with the brachial artery, it passes through the triangular space formed by the long head of the triceps muscle, the humerus bone and the teres major. It enters the spiral groove located posteriorly on the proximal part of the humerus. As it passes through the groove, it travels with deep brachial artery between the medial and long heads of the triceps muscle. During its course here, it gives two sensory branches, posterior antebrachial cutaneous nerve and the inferior lateral brachial cutaneous nerve. These two innervates the posterior forearm and the lower lateral part of the arm respectively. Radial nerve wraps around the humeral shaft as it moves from posterior to anterior within the groove. Here it pierces the lateral intermuscular septum and reaches the anterior compartment. It runs between brachial and brachioradial muscles in the cubital fossa. At the elbow level, after passing anterior to the lateral epicondyle of the humerus, it gives its superficial sensory branch and becomes the posterior interosseous nerve (PIN). The muscles it innervates before forming the PIN are the triceps, brachioradialis, anconeus and extensor carpi radialis longus (ECRL). The superficial sensory branch runs deep to the brachioradialis. It crosses the anatomical snuffbox distally and innervates the radial side of the dorsum of the hand and the dorsal surface of the first 3.5 fingers.[3,19,25-27]

Shortly after its formation, the PIN pierces the supinator muscle. Here, the thick proximal edge of the superficial head of the supinator is called the Frohse arc. After piercing the supinator, it moves between the deep and superficial heads of the muscle. Then it pierces the muscle again and enters the posterior compartment. After that it divides into two branches (medial and lateral) which innervates most of the forearm and hand extensor muscles.[3,19,25,27]

Radial nerve can be trapped at three sites: above the elbow, after becoming PIN and around the wrist. Above-elbow compression can occur in the axilla, spiral groove or rarely in the triangular interval. The chronic compression at the axilla level is called "crutch paralysis" while the acute form is called "saturday night paralysis". Crutch paralysis is caused by prolonged, inappropriate use of the crutch. In saturday night paralysis, the same compression develops acutely as a result of the patient falling asleep with their arm hanging down from the back of the chair. Drop hand Syndrome which the wrist and fingers cannot be extended. Sensory deficit occurs in all of the areas innervated by radial nerve. Elbow extension is impaired. The prognosis in these cases are generally good

as the nerve damage is usually at the level of segmental demyelination. In most cases, full recovery occurs within 2-3 months. In case of inadequate recovery, needle EMG examination at 12th week helps to evaluate prognosis.[3,19,25-28]

Compression on the spiral groove is usually caused by humeral shaft fractures. This group accounts for 70% of compression neuropathies of the radial nerve. Usually the injury is acute. The compression may originate from the fracture itself or, more frequently may be iatrogenic after correction surgery. Chronic entrapment may occur in intermuscular septum due to insufficient mobility after fracture and lateral head of the triceps after prolonged stretching exercise. Callus formation after fracture and fibrosis in the muscle due to chronic intramuscular injection may be possible causes for chronic entrapment Symptoms are similar to that of entrapment at the axilla level, but there are some differences. Here elbow extension is preserved since triceps is spared; but the forearm cannot be pronated or supinated while the elbow is in extension. In addition, while there is a sensory deficit in the distal forearm; sensation of the arm's posterior is preserved.[28,29]

Entrapment of PIN most commonly occurs when Froshe's arch thickens as a result of repetitive pronation supination movement. Less common sites of compression are the radial artery crossing the radial neck (Henry's leash), the distal end of the supinator, extensor carpi radialis brevis (ECRB) and cysts seen in rheumatoid arthritis. On rare occasions, the nerve may also be compressed after it divides into two branches. In PIN compression, there is typically weakness in finger extension. But wrist extension can be achieved by radially deflecting the wrist because ECRB and ECRL is spared. Atrophy develops at the forearm extensor muscles. There may or may not be mild pain in the lateral forearm. There is no sensory deficit.[19,30]

Here, the level of nerve compression can be understood by detecting the affected muscles. If ECU, extensor digitorum quadratus (EDQ) and extensor digitorum communis (EDC) are affected, it suggests that the medial branch is affected. If abductor pollicis longus, extensor pollicis brevis (EPB), extensor pollicis longus (EPL) and extensor indicis proprius (EIP) are affected, it suggests that the lateral branch is affected. If all of them are affected, it suggests that the PIS is affected at a level before it is divided into branches.[30]

The path of the radial nerve from the radial head to the distal end of the supinator muscle is called radial tunnel. Its borders are drawn by the supinator muscle, ECRL, ECRB and brachioradialis. Radial tunnel syndrome (RTS) is a condition characterized by isolated pain without muscle weakness or sensory deficit caused by recurrent mild compression of PIN within the tunnel. Tenderness over the radial nerve trace '5 cm'can be erased distal to the lateral epicondyle is the main symptom.

The pain worsens at night, may awaken the patient from sleep and may be aggravated by nerve-straining maneuvers such as elbow extension, forearm supination or wrist hyperextension. EMG findings are normal. MRI results are normal or shows nonspecific changes in most cases. The diagnosis is made by excluding alternative diagnoses.[31]

CONCLUSION

Entrapment neuropathies are conditions in which damage is often reversible with early recognition. Careful differential diagnosis and determination of treatment strategy before permanent deficits develop will reduce morbidity rates significantly.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review

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Is functional MRI meaningful in migraine?

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ABSTRACT

Functional magnetic resonance imaging (fMRI) is an imaging method that enables us to understand brain anatomy, mapping and its function. While fMRI was previously used in experimental studies, it has now been used in clinical studies. Imaging in fMRI is based on measuring the increase in regional blood flow caused by cortical activation. fMRI indirectly demonstrates neural activation by detecting increases in oxygenation. fMRI relies on the sensitivity of magnetic resonance signals to changes in deoxyhemoglobin levels or perfusion, reflecting the metabolic and hemodynamic responses associated with neural activation. Imaging is arranged in the clinic for primary headaches if needed for a differential diagnosis. However, imaging studies are utilized in scientific research to elucidate the pathophysiology. Migraine is a common episodic disorder characterized by recurring attacks. Investigating the functional structure of the brain during both attack and interictal periods is crucial in understanding migraine pathology. However, capturing patients' migraine attacks for monitoring purposes without treatment is considered unethical in many countries. Moreover, conducting such studies is hindered by the requirement for prolonged hospital stays and extended imaging times, which significantly increase costs. Despite the challenges of conducting research in migraine patients, fMRI stands out as an excellent imaging method for investigating the functional brain structures involved in this episodic disorder. Several fMRI studies have yielded valuable insights into the pathophysiology of migraine. fMRI is believed to offer valuable guidance in refining our understanding of migraine-specific mechanisms, facilitating biomarker studies for migraine activity, and elucidating abnormal functions in regions affected by migraine. Monitoring treatment response using biomarkers is anticipated to be an effective tool for identifying targets for migraine treatment, including assessing treatment efficacy in the development of new migraine-specific therapies.

Keywords: Migraine, functional magnetic resonance imaging, pathophysiology

INTRODUCTION

The function of the brain and the mapping of these functions are fundamental topics in neuroscience.Traditional electrophysiological methods such as electroencephalography (EEG), electrocorticography (ECoG), and invasive EEG can illuminate the temporal dimension of brain functions, but only a rough idea can be obtained about neural localization. The cortex has high spatial complexity; the spatial resolution of surface EEG is weak, and the resolution of invasive electrodes is high but risky. Magnetoencephalographic methods combine the superior temporal resolution of EEG with high spatial resolution. However, due to being outside the skull, the sub-centimeter 5 mm and millisecond-level 1 ms temporal resolution include projection errors. The ability to record deep sources is limited. Nuclear imaging methods indirectly reveal regional blood flow, regional metabolic activities, and brain activation. Although SPECT and PET can sometimes be combined with computerized tomography (CT) and magnetic resonance imaging (MRI), the disadvantage of these techniques is the use of radioactive substances as biomarkers. They are not suitable for studies with healthy control groups and repetitive scientific studies but are suitable for experimental designs.[1]

As for Functional MRI (fMRI), this technique is a method that reveals brain anatomy with excellent spatial resolution. The combination of high spatial resolution with high temporal resolution has made brain mapping possible. fMRI not only allows the localization of simple sensory-motor activations but also enables the localization of cognitive processes. Cortical activation mapping is achieved by obtaining physiological data through non-invasive methods.[2] Since the year 2000, fMRI has transitioned from an

experimental method to being used in clinical studies. Being the most powerful tool used in mapping neural activities of the human brain, functional MRI (fMRI), was first studied in healthy individuals in areas such as vision, motor function, language, memory, emotion, and pain. Subsequently, studies have been conducted on conditions including stroke, epilepsy, multiple sclerosis, psychiatric disorders, and migraine, and it is used before brain surgery operations.[3] Initially, exogenous biomarkers were administered, and the temporal changes in their concentrations in the brain were recorded. The rate and amount of concentration change were then used to calculate regional cerebral blood flow, an indirect indicator of neural activation.

When it was discovered that endogenous deoxy-Hb could be used as a biomarker, the use of exogenous biomarkers was abandoned. Other blood spins have endogenous techniques, but they are not used due to their simpler mechanism and lower temporal resolution. Cortical activation leads to an increase in regional cerebral blood flow. With fMRI, the increase in oxygenation is detected, indirectly revealing neural activation. Regions with oxygen increase are seen as bright areas in structural images, and this method is called blood oxygen level-dependent enhancement (BOLD). Oxyhemoglobin is diamagnetic for biological tissues, so it does not affect the signal from the tissue. Deoxyhemoglobin, on the other hand, is paramagnetic, shortening the magnetic relaxation time and changing the signal intensity. In areas of brain activation, oxygen consumption rate increases. Oxyhemoglobin increases in active areas, while deoxyhemoglobin decreases. Thus, by detecting both the brain regions and the differences in activity within these regions during a mental task, various activation patterns associated with different functions in the brain can be identified.[4] In summary, fMRI is structured on the fact that magnetic resonance signals are sensitive to deoxyhemoglobin or perfusion changes that accompany metabolic and hemodynamic responses resulting from neural activation. Various brain functions such as motor, speech, and vision can be evaluated by assigning tasks. Increased activity in neurons undergoing activation leads to higher energy demands due to activities such as neurotransmitter release, action potential transmission, and maintaining ion balance, enabling functional imaging of the brain regions involved in performing the given task through increased blood flow. Resting State fMRI method is used for brain mapping obtained at rest, without being assigned a task. With this technique, networks are displayed, and connectomes are analyzed.[5]

In clinical practice, imaging is used for differential diagnosis in primary headaches, while in scientific studies, it is used to elucidate the pathophysiology. For this purpose, transcranial magnetic stimulation, PET, and increasingly, fMRI are being utilized. MRI is the preferred imaging modality due to its high resolution, low cost, lack of radiation, and repeatability for studies.[6,7]

The use of fMRI in the field of migraine has provided data for illuminating the pathophysiology of this condition. It has contributed to better defining specific mechanisms of migraine, conducting biomarker studies for migraine activity, and shedding light on atypical functions in regions exhibiting abnormal function in migraine. It is believed that fMRI can be an effective tool in studies aimed at determining targets for migraine treatment, such as imaging treatment response with biomarkers and developing new migraine-specific treatments based on treatment response.[8]

International Classification of Headache Disorders (3rd edition) defines migraine as a disorder consisting of five phases: asymptomatic period, prodromal period, aura period, headache period, and postdromal period. In functional imaging studies, three of these phases—asymptomatic, prodromal, and postdromal—are defined as the "interictal period," while aura and headache are defined as the "ictal period." In brain imaging studies with functional MRI, two types of fMRI have been used in migraine: Task-based fMRI and Resting-state fMRI. Both receive BOLD signals. 3D images of the brain are structured with voxels called small cubes.[8,9]

Task-based fMRI evaluates the activity of specific brain regions stimulated by an external stimulus. Visual rotating checkerboard or intranasal trigeminal stimulation can be used as stimuli. Increased BOLD signal indicates increased neuronal activity, while decreased signal indicates decreased activity. The obtained results are sometimes compared with those obtained from healthy controls and sometimes with the patient's interictal period.[9]

Resting-state fMRI, typically conducted while the patient lies in the scanner with eyes closed and no external stimuli, aims to capture brain activity during rest. Specific anatomical information is predefined, and BOLD signals from two brain regions showing synchronization are functionally connected areas. Increased synchronization in the frequency of BOLD signal indicates increased functional connectivity in the given network, while a decrease indicates decreased functional connectivity.[9]

FUNCTIONAL MRI STUDY DESIGN AT MIGRAINE

Three main study models have been used to conduct fMRI in migraine. The first two are designed as case-control models, where asymptomatic (or rarely headache-prone) migraine patients are tested with fMRI on a headache-free day and during an attack, compared with healthy controls. The third model involves evaluating migraine by provoking it. In this model, typical prodromal, aura, and headache stages in the same patient are compared with the asymptomatic phase of the same patient. Many studies have been conducted using agents such as nitroglycerin, CGRP, and PACAP in this model. Additionally, this model can be used to investigate the side effects of drugs and their effects on brain functions.[10-13]

Most studies have been conducted during the asymptomatic phase. The absence of pain that would prevent patient participation has made imaging and studies most feasible. Numerous studies during the asymptomatic phase have shown functional reorganization at both cortical and subcortical levels contributing to abnormal sensory processes in migraine patients using fMRI.[14] Functional changes observed during the asymptomatic phase have been thought to represent the characteristics of the brain that predispose

individuals to migraine. These changes have been primarily observed in the thalamus, periaqueductal gray matter, insula, somatosensory, prefrontal, and anterior cingulate cortex, and it is accepted that they cause disorders in the processing of pain sensory, emotional and cognitive perspectives.[15,16]

Moreover,abnormalities in visual processing and hyperexcitability in the visual cortex have been detected in migraine patients in fMRI and PET studies conducted during the asymptomatic phase.[17,18]

In the literature, there are also studies in which no functional differences were found during the asymptomatic phase. This might be explained by factors such as the clinical characteristics of patients, groups with low frequency of pain, or short-duration disease. Additionally, it is suggested that functional interactions between brain regions involved in pain and visual function may develop over time.[19]

IMAGING DURING THE PRODROMAL PHASE AND EARLY ATTACK PHASE

Complaints such as yawning, difficulty concentrating, and pallor described by patients before the onset of headache are now accepted as indicative of a prodromal phase of migraine. Studies examining this period are limited. In a recent study where Pituitary Adenylate Cyclase-Activating Polypeptide-38 (PACAP38) and Vasoactive Intestinal Peptide (VIP) were used as triggers, the early stage of migraine attack was investigated. Disturbances, particularly between the somatosensory and visual cortices, were found during the prodromal period in patients triggered by PACAP38. Another study on the prodromal phase, where headache was triggered by glyceryl trinitrate, showed changes in hypothalamic activity.[20,21]

IMAGING DURING THE AURA PHASE

Aura, the shortest phase of migraine, is therefore a challenging area for neuroimaging studies. This phase, which rapidly begins and concludes within minutes, can manifest as typical positive visual disturbances (scintillation) or negative visual disturbances (scotoma), and in some patients, sensory symptoms may follow visual symptoms. Imaging was performed before, during, and after visual aura onset. One of the most important results obtained from this study was perhaps the pattern of spread of the BOLD response, which supported the cortical spreading depression theory. The first observed BOLD changes in the extrastriate cortex, an increase and subsequent decrease in cerebral blood flow, were consistent with the findings of the study conducted by Lauritzen et al.[22] using SPECT.

IMAGING DURING HEADACHE

Headache, typically lasting 4-72 hours with moderate to mild intensity and accompanied by nausea and photophobia, is a typical example of migraine. Imaging during headache is a challenging phase to study because it would require depriving the patient of treatment.[23] In a study evaluating nine patients with task-based functional MRI imaging methods for 30 days, changes in hypothalamic excitability were investigated, but no significant results were obtained. However, another resting-state fMRI study found changes in right thalamocortical connections.[24] In another study examining migraine headache triggered by GTN, a significant relationship between the somatosensory cortex and pons was found during the headache phase.[25]

IMAGING DURING THE POSTDROMAL PHASE

Symptoms vary widely, but some migraine patients describe postdromal complaints such as difficulty concentrating, neck pain, and fatigue after the headache. Conducting studies during this phase is ethically challenging as the duration is undefined and treatment may still be required, similar to the headache phase. It is known that this phase lasts less than 6 hours in 50% of patients. In a study focusing only on hypothalamic changes during the postdromal phase, it was found that the response to pain stimuli in the visual cortex was higher than during the headache phase.[26]

Only one study examined a patient during the postdromal phase using resting-state fMRI, but no difference was found compared to the asymptomatic phase. Hyperexcitability was also observed in the visual cortex [24] hours after the pain subsided, and it was interpreted that these findings could explain the continued light sensitivity in some patients after the pain has resolved.[27]

MIGRAINE FMRI: CONTRIBUTIONS AND POTENTIAL

In studies involving sensory stimuli, atypical responses of the migraine brain, the lack of expected normal habituation response between attacks, and atypical functional connections in sensory processing are recognized as established migraine pathophysiological features.[28]

In individuals with visual aura migraines, disruptions in cognitive and limbic connections, abnormal function in the visual cortex, marked light sensitivity, and involvement of the brainstem and hypothalamus at the onset of attacks have been demonstrated.[29]

The anterior insula plays a significant role, particularly in migraines with aura, in autonomic and sensory functions. This region, which controls cardiovascular parasympathetic tone, may be related to the cardiovascular features of migraine.[30]

Transcutaneous vagus nerve stimulation has been shown to modulate the thalamocortical pathway in migraine patients, emphasizing the role of fMRI in developing and testing treatment options.[31]

CONCLUSION

Despite the lack of an optimal method for fMRI studies and the weak statistical power based on the small number of patients, these studies have facilitated our understanding of many pathophysiologies in migraine. As prospective models of these studies increase over time, which enables to identification of specific markers for migraine and

determining target points for treatment, it is believed that they may shed light on the pathophysiology of migraine, which ranks high in terms of disability.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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Associated with hyperglycemia: a rare cause of hyperkinetic movement disorders

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ABSTRACT

Diabetic striopathy, a neurological disorder associated with diabetes mellitus, is characterized by specific changes in basal ganglia structures, particularly the striatum. Although its precise etiology remains elusive, chronic hyperglycemia, microvascular dysfunction, oxidative stress, and inflammation are implicated. Diagnosis relies on clinical assessment and neuroimaging, revealing characteristic basal ganglia abnormalities. Management focuses on optimizing glycemic control and alleviating symptoms. We present an 83-year-old woman with abrupt-onset unilateral chorea-ballismus as a case illustration, showcasing diagnostic and therapeutic approaches. Understanding the underlying mechanisms and refining management strategies are crucial for effectively addressing this complex neurological complication of diabetes mellitus.

Keywords: Hyperglycemia, striatopathy, diabetic ketoacidosis

INTRODUCTION

Diabetic striopathy, also known as diabetic striatal syndrome or diabetic striatal degeneration, is a neurological disorder characterised by specific changes in the basal ganglia structures, particularly the striatum, in individuals with diabetes mellitus.[1,2] It is considered a relatively rare complication of diabetes, predominantly affecting individuals with long-standing and poorly controlled diabetes.[3]

The pathogenesis of diabetic striopathy is not yet fully understood, but it is believed to be multifactorial. Chronic hyperglycemia, microvascular dysfunction, impaired blood-brain barrier integrity, oxidative stress, and inflammation have been implicated as potential contributors to the development of this condition.[4,5]

It has usually been described in elderly females with hyperglycemic hyperosmolar states, but instances in patients with diabetic ketoacidosis are few. Clinically, diabetic striopathy presents with various neurological symptoms, including movement disorders such as chorea, dystonia, or parkinsonism. These movement abnormalities may be accompanied by cognitive impairment, psychiatric symptoms, and autonomic dysfunction. The severity and progression of symptoms can vary among individuals.[6]

The diagnosis of diabetic striopathy is typically based on clinical evaluation, neuroimaging studies. It can be shown to have reversible hipodensity in the corpus striatum on computer tomography (CT) and hyperintensity on brain magnetic resonance imaging (MRI), with the exclusion of other possible causes of basal ganglia dysfunction.[7,8] Neuropathological studies have revealed characteristic findings in the striatum, such as gliosis, neuronal loss, and vascular changes.[9]

Management of diabetic striopathy primarily focuses on optimising glycemic control and addressing associated comorbidities. Symptomatic treatment may include the use of medications to manage movement disorders or psychiatric symptoms. However, the effectiveness of specific therapies remains limited, and further research is needed to establish optimal treatment strategies.[6]

CASE

A 83-year-old woman with a history of type 2 DM presented with abrupt-onset unilateral chorea-ballismus. Symptoms started with abrupt-onset choreiform movements on the left-sided extremities lasting three weeks.

Her medical history included hypertension, atrial fibrillation, and a previous stroke with no residual disability. She doesn't have a history of movement disorders or epilepsy. Records revealed capillary blood glucose (CBG) of 565 mg/dl, urine glucose +++, urine ketone was negative, and a venous blood pH value of 7.4 with a high serum osmolarity of 303 mOsm/kg and normal renal and liver function tests. The patient was diagnosed with non-ketotic hyperglycemia. A brain CT showed slightly high attenuation of the right putamen and globus pallidus Figure 1.A. Brain MRI revealed an area of high signal intensity in T1-weighted images Figure 1.C and low signal intensity in FLAIR images Figure 1.B, involving the right putamen and globus pallidus. Diffusion-weighted MRI brain images did not reveal any abnormal restricted diffusion in the right basal ganglia Figure 1.D.

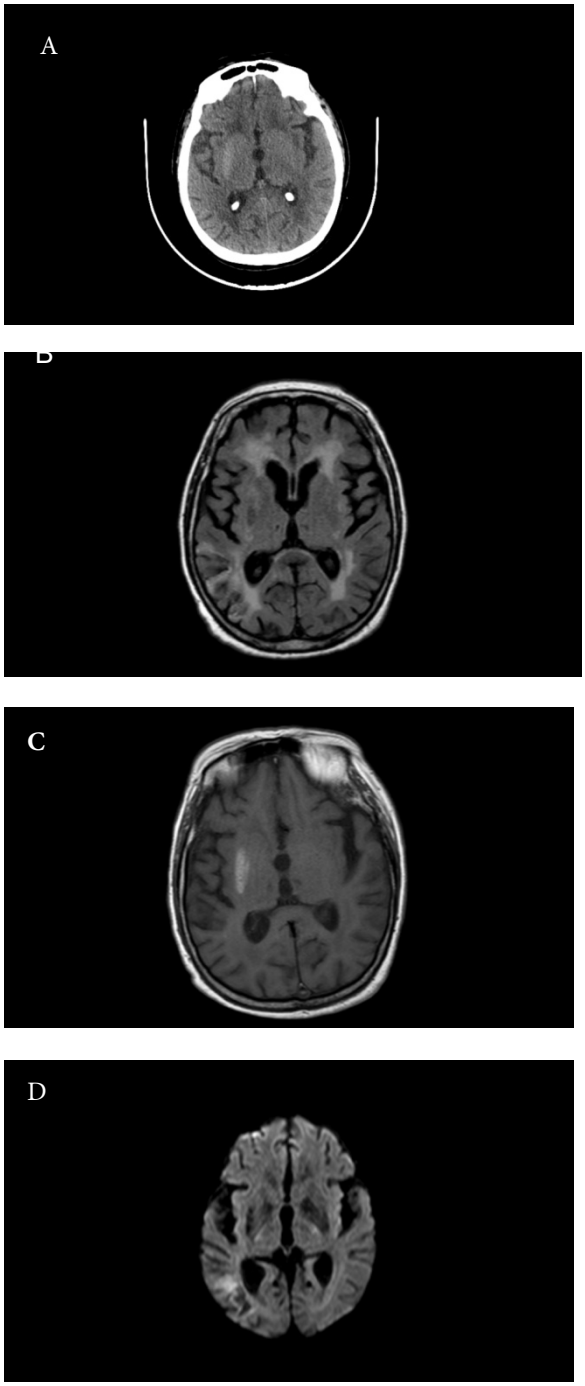

Figure 1. (A-D) (A) A brain CT scan revealed slight attenuation of the right putamen and globus pallidus shows with white arrow (B) FLAIR images showing hypointensities and (C) T1 weighted images with white arrow shows hyperintensities in the right lenticular nucleus (D) Diffusion Weighted MR image demonstrating no diffusion restriction.

According to the blood sugar measurements, insulin treatment has been planned for the patient. Moreover, the initial treatment for the involuntary movements is 5 mg of haloperidol twice a day. But it wasn't efficient, so we added ketiapin 25 mg twice a day. After this change, involuntary movements decreased, but they were still continuing. Two weeks after the admission, involuntary movements totally disappeared, and we stopped haloperidol and planned to reduce the ketiapin dosage in a 1-3 month follow-up. We are scheduled for a revaluation and repeat imaging after 3 months. A follow-up brain MRI after 3 months of treatment showed improved signal abnormalities at the right globus pallidus and putamen Figure 2, B-C. Also, a control brain CT showed a decrease in the size of the hyperdensity Figure 2.A.

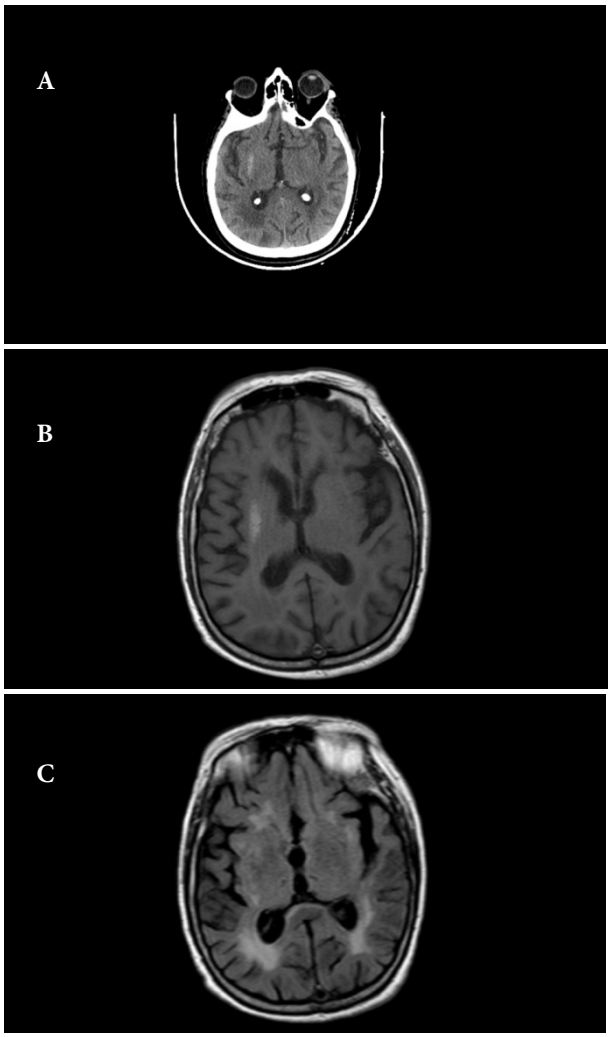

Figure 2. (A-C) (A) Control CT image showing the decrease in the size of hyperdense lesion in the right basal ganlia. (B-C) Control brain MRI (T1 wegihted image: B, FLAIR image: C) showing slight decrease in abnormal signal intensities.

DISCUSSION

Diabetic striopathy is a complex neurological disorder associated with diabetes mellitus, characterised by specific changes in the basal ganglia structures, particularly the striatum. Although the exact pathogenesis of diabetic striopathy is not fully understood, several mechanisms have been proposed based on existing literature.

Chronic hyperglycemia has been identified as a key factor in the development of diabetic striopathy. Prolonged exposure to high glucose levels can lead to oxidative stress and the

formation of advanced glycation end products (AGEs), which contribute to neurovascular dysfunction and neuronal damage within the basal ganglia structures.[10] Microvascular dysfunction, including endothelial dysfunction and blood-brain barrier impairment, has also been implicated in the pathogenesis of diabetic striopathy.[11] These vascular abnormalities can lead to compromised perfusion and nutrient supply to the basal ganglia, resulting in neuronal loss and gliosis.

Inflammation is another potential contributor to the development and progression of diabetic striopathy. Chronic low-grade inflammation is commonly observed in diabetes mellitus and has been linked to neuroinflammation and neurodegeneration.[12] Inflammatory mediators, such as cytokines and chemokines, may play a role in the disruption of the basal ganglia structures and the development of movement disorders seen in diabetic striopathy.

Genetic factors may also influence the susceptibility to diabetic striopathy. Studies have identified specific gene variants associated with an increased risk of developing movement disorders in individuals with diabetes.[13] However, further research is needed to elucidate the genetic underpinnings of this condition and their interaction with environmental factors.

The diagnosis of diabetic striopathy relies on clinical evaluation, neuroimaging findings, and the exclusion of other potential causes of basal ganglia dysfunction. Neuroimaging techniques, such as MRI or CT, can reveal characteristic changes in the striatum, including atrophy, signal abnormalities, and vascular lesions.[14]

Management of diabetic striopathy focuses on optimising glycemic control and addressing associated comorbidities. Intensive glucose management and control of other cardiovascular risk factors may help slow the progression of neurological symptoms.[15] Symptomatic treatment with medications targeting movement disorders, such as dopaminergic agents or antipsychotics, may be considered on a case-by-case basis, taking into account the individual patient's needs and risks.

CONCLUSION

Diabetic striopathy is an intriguing neurological complication of diabetes mellitus, characterised by distinct changes in the basal ganglia structures. Management involves optimising glycemic control and addressing associated comorbidities. Understanding the underlying mechanisms and improving diagnostic and therapeutic approaches are crucial for better management of this condition.

ETHICAL DECLARATIONS

Informed Consent:

The patient signed and free and informed consent form.

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The authors have no conflicts of interest to declare.

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Author Contributions:

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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A rare case of hereditary ataxia: Gordon Holmes syndrome

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ABSTRACT

Gordon Holmes syndrome is an extremely rare, autosomal recessive condition with characteristic features of cerebellar progressive ataxia, cerebellar atrophy, and hypogonadotropic hypogonadism, which was first described in 1908 by the British neurologist of the same name. Two genes have to date been frequently associated with this syndrome, RNF216 and PNPLA6.[1] A 23-year-old man presented with secondary sexual character deficiency and progressive difficulty in gait persisting for several years. He was eventually immobilized after seven years of ongoing symptoms and was definitively diagnosed with Gordon Holmes syndrome after genetic testing revealed RNF216 gene mutation.

Keywords: Cerebellar ataxia, ubiquitin, RNF216, neuroendocrinology

INTRODUCTION

Gordon Holmes syndrome, an autosomal recessive, adult-onset condition marked by progressive cognitive decline, dementia, ataxia, and chorea, in addition to hypogonadotropic hypogonadism, was first described by the British neurologist of the same name in 1908.[2] Holmes made major contributions to the study of cerebellar physiology and challenged the current conventional ideas regarding the unitary physiology of the cerebellum, even during the First World War, when he served as consultant neurologist to the British Army on the Western Front. He was subsequently awarded the CMG and CBE and was knighted in 1951. After the war, he published comprehensively in the field of neurology, and was actively engaged in neurological practice, research and education.[2]

Several studies have shown that the initial symptoms of this syndrome appear in early adolescence and present as difficulty in speaking.[3] Mutations in either the RNF216 or PNPLA6 genes are thought to represent the underlying cause of Gordon Holmes syndrome, although there are rare instances in which no mutation has been identified. The underlying pathophysiology involves mutations in these particular genes, which cause ubiquitin to bind to healthy proteins and induce apoptotic processes, leading to cell death.[4] This cell death may lead to progressive ataxia, hypogonadotropic hypogonadism, and structural changes in the brain such as cerebellar atrophy and white matter lesions.[1] However, due to its rarity and frequent misdiagnosis, the prevalence of Gordon Holmes syndrome remains unknown.

A SHORT OVERVIEW OF THE RECENT LITERATURE ON GORDON HOLMES SYNDROME

Gordon Holmes syndrome, also known as autosomal recessive spinocerebellar ataxia type 16 (SCAR16), was first described in 1908.[2] Although nearly 110 years have since passed, to our knowledge there are still only 10 case reports in the literature. The most recent reported case is located in India with homozygous mutation for RNF216, a 30-year-old male patient with progressive ataxia and hypogonadotrophic hypogonadism.[5] Neuroimaging in that case revealed hyperintensities in the white matter in FLAIR-MR images.[3] Chiu et al.[6] described a patient from Taiwan with cerebellar ataxia and mutation in STUB1, another gene that can lead to Gordon Holmes syndrome. In 2019, another case was reported exhibiting classic Gordon Holmes syndrome symptoms of ataxia, amenorrhea, and cerebellar syndrome.[3] That case was similar to that of a 26-year-old man reported in 2018, who presented with slowly progressing loss of balance and speech difficulty with hypogonadotropic hypogonadism.[1] However, the diagnosis was unfortunately not confirmed by

genetic testing, indicating the critical importance of genetic testing for hereditary syndromes characterized by cerebellar ataxia multisystem presentation.[1]

CASE

A 23-year-old man presented to his family physician prior to military duty and was referred to our neurology clinic for further evaluation because of ataxia. In 2018, he was admitted to the endocrinology clinic with growth retardation and gynecomastia, as well as hypogonadotropic hypogonadism, resulting in a decision to initiate monthly sustanon therapy, which proved to be ineffective. His detailed clinical history revealed a progressive speech disorder beginning at the age of 18, along with difficulties in walking and ataxia over the following two years that resulted in an inability to walk without assistance. The patient was born by the spontaneous vaginal route, with no consanguinity between his parents and no personal history of birth trauma or neurological disease. Neurological examination revealed hyperactive deep tendon reflexes in the lower limbs with relatively preserved upper deep tendon reflexes. Cerebellar examination revealed dysmetria, dysdiadochokinesia, and dysarthria, as well as a pathological tandem gait marked by wide-step walking. Routine blood tests were normal, but hormonal tests revealed hypogonadotropic hypogonadism and low follicle-stimulating hormone, luteinizing hormone, and testosterone levels (Table).

Table. Patient's blood test results

Parameters	Results	Reference values
FSH	<0.30 mIU/mL	1.9-18.9 mIU/mL
LH	<0.07 mIU/mL	1.7-9.6 mIU/mL
GH	0.16 µg/L	0.003-0.971 µg/L

(FSH: Follicle-Stimulating Hormone LH: Luteinizing Hormone GH: Growth Hormone)

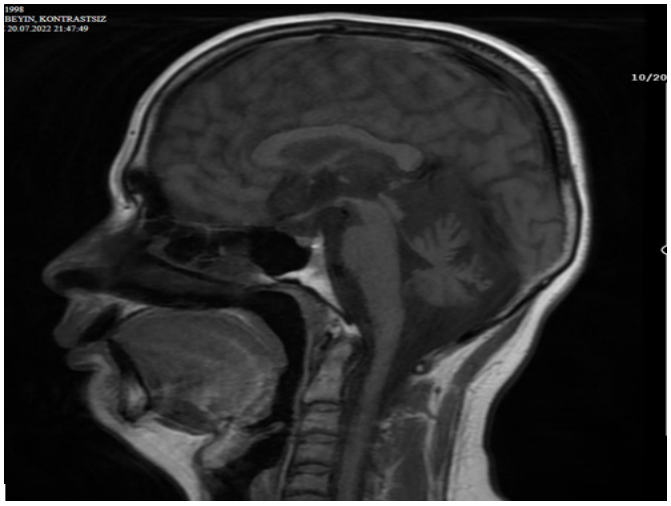

Figure 1. Magnetic resonance image without contrast showing aberrant cerebellar atrophy

An increased amount of cerebrospinal fluid was observed around the cerebellum and between the cerebellar folia (cerebellar atrophy), the third and lateral ventricles were enlarged, and hyperintense signal changes consistent with gliosis areas were present in bilateral periventricular white matter. Subsequent genetic testing revealed a homozygous RNF216 mutation.

The patient was in followed-up in the neurology and endocrinology outpatient clinics for three-month periods. Patient was informed and written consent was obtained.

DISCUSSION

Cerebellar ataxia is fairly common complaint in neurological outpatient clinics, and usually results from infections, cerebrovascular diseases, metabolic imbalances, and genetic causes.[1,9] Gordon Holmes syndrome is one of the rare genetic causes of cerebellar ataxia, and is inherited in an autosomal recessive manner due to mutations in specific genes, such as RNF216, PNPLA6, STUB1, and OTUD41; From the pathophysiological perspective, these mutations lead to the activation of the ubiquitination cascades8, triggering a proteolytic/apoptotic process, finally presenting with slowly progressing ataxia, cerebellar atrophy, dementia, and hormonal changes characterized by hypogonadotropic hypogonadism (Figure 2).[1,4]

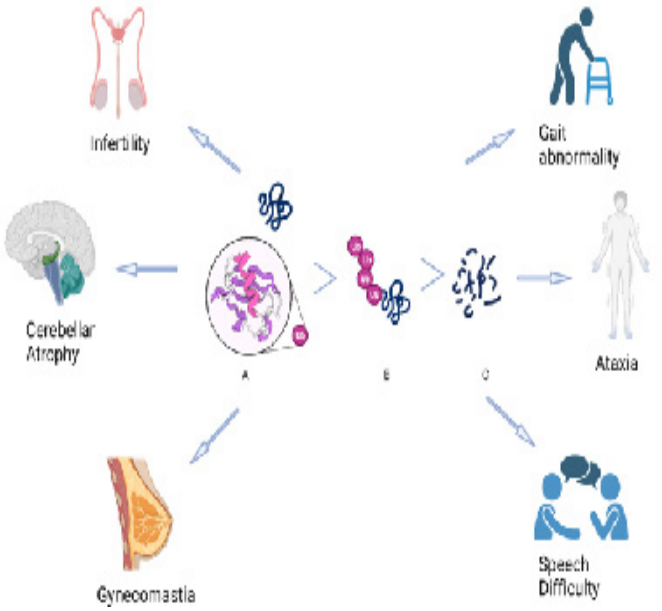

Figure 2. The ubiquitination process in Gordon Holmes syndrome, A: A healthy protein and ubiquitin, B: Ubiquitin binds to healthy protein and causes degradation of the protein C: Protein degradation and the symptoms of Gordon Holmes syndrome.[10]

Several studies have shown that the underlying pathophysiology also causes neurodegeneration in numerous regions of the brain, such as white matter, the hippocampus, and the pituitary gland.1 In our case, we found a homozygot RNF216 mutation (c.1860_1861dupCT) which caused hypogonadotrophic hypogonadism, progressive ataxia which leads to walking difficulties and white matter hyperintensities.

THE PATHOPHYSIOLOGCAL IMPORTANCE OF RNF216 (RING FINGER PROTEIN 216) GENE IN GORDON HOLMES SYNDROME

RNF216 is an E3 ubiquitin ligase, also known as TRIAD3, which regulates cell death and is one of the genes responsible for Gordon Holmes syndrome.[4] It also deserves greater attention for a better understanding of the pathophysiology of the disease. Recent studies have suggested that RNF216 is an important gene for meiosis, implicated in spermatogenesis

and the male reproduction system.[7] Melnick et al.[4] studied tissue RNF216 concentrations in rodents and found that expression commenced at one week, being observed in most tissues, including the heart, liver, and lung, with the highest levels being found in the testis. Those authors also found that RNF216 was only crucial for male reproduction, since the mutations seemed to have no effect on females.[4] As shown above, RNF216 can be detected in numerous tissues, including the central nervous system.[4,8] A good example is a recent study by Chen et al.[7], who evaluated the role of RNF216-mediated cell death in patients with subarachnoid hemorrhage and observed increased RNF216 in subarachnoid hemorrhage leading to neuronal damage. Those authors also noted that reducing the expression of the gene protected the neurons from apoptosis and lowered the level of brain injury.[7] It should also be remembered that RNF216 mutation can cause Huntington-like disorder. A case report of Huntington-like disorder with RNF216 gene mutation described patients from two Belgian families who presented with Huntington-like chorea.[4] The authors noted a distinction in terms of inheritance, with a Huntington-like phenotype occurring if the mutation is monogenic, whereas oligogenic inheritance leads to Gordon Holmes syndrome. In addition to its role in reproduction and neuronal systems, RNF216 is also involved in malignancy processes. For instance, Xie et al.[8] observed overexpression of RNF216 in glioblastoma multiforme specimens, which may be indicative of poorer prognosis.

This case report describes a 23-year-old man who presented to our outpatient clinic with progressively worsening difficulty in walking over the previous five years and who was diagnosed with Gordon Holmes syndrome with RNF216 mutation.

There are currently no therapeutic options available for the syndrome, with the exception of symptomatic treatments such as hormonal therapy, which lead to only partial improvement in some patients.1

CONCLUSION

To summarize, we describe a patient with Gordon Holmes syndrome which is a rare disorder manifested with ataxia and hypogonadotropic hypogonadism, reported from Turkiye and one which adds to our knowledge of the ethnic distribution of the RNF216 mutation, along with a brief review of the subject.

ETHICAL DECLARATIONS

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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Os odontoideum with progressive symptoms: case report

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ABSTRACT

A 53-year-old male patient was admitted to the neurosurgery outpatient clinic with neck pain. He had difficulty performing fine manual skills, had numbness in his hands, and felt as if he was stepping on a space while walking. He declared that his head occasionally fell forward involuntarily. He had no urinary or fecal incontinence or neurogenic claudication. On neurologic examination, there was no loss of muscle strength and no pathologic reflex. He was skillful in cerebellar tests. He declared no history of falls, impacts, or accidents. From the patient's hospital digital records, it was seen that he was admitted to the neurosurgery outpatient clinic with right arm and neck pain before, and surgical treatment was recommended to him due to the os odontoideum, but he refused this treatment. As the patient became symptomatic in the following period, atlantoaxial instability was found on cervical dynamic X-rays. For all these reasons, he was advised to undergo surgical treatment, but he re-refused the operation. In conclusion, it was considered that close follow-up with conservative treatment in asymptomatic os odontoideum patients may be appropriate. However, it was suggested that the possibility of AAI should be considered in patients who become symptomatic.

Keywords: Os odontoideum, atlantoaxial instability, conservative treatment, surgery

INTRODUCTION

Os odontoideum (OO) is an anatomical variant of the C2 dens, defined as an independent ossicle of variable size with smooth circumferential cortical edges separated from the axis.[1] Congenital and acquired causes are discussed in the etiology of os odontoideum and there is still no clear information about its epidemiology. Patients with os odontoideum may be asymptomatic or present with a spectrum of neurologic deficits. Conservative treatment is recommended for asymptomatic patients, while surgical treatment is recommended for symptomatic patients.[2] In this case report, a patient with os odontoideum is discussed.

CASE

A 53-year-old male patient was admitted to the neurosurgery outpatient clinic with neck pain which had been present for 4 years but had intensified in the last 1 month. He declared difficulty in performing fine manual skills such as buttoning buttons and zipper pulling, numbness in his hands, and felt as if he was stepping on a space while walking. He also declared that his head occasionally fell forward involuntarily. He had no urinary or fecal incontinence or neurogenic claudication. He had no history of falls, impacts, or accidents. On neurologic examination, it was observed that his cervical posture was impaired; his head was turned forward and slightly to the right in its natural position (torticollis). His muscle strength was normal, but his biceps and patella reflexes were hyperactive. No pathologic reflex (such as Babinsky's sign or Hoffman's sign) was detected. He was skillful in cerebellar tests.

When the patient's hospital digital records were analyzed, it was seen that the brain magnetic resonance (MR) images performed five years ago for headache showed findings os odontoideum and myelomalacia in the spinal cord at that segment. It was also seen that at that time, he was admitted

to the neurosurgery outpatient clinic with right arm and neck pain, his neurological examination findings were found normal, and the os odontoideum and myelomalacia in the spinal cord were also seen in the cervical MR images. Surgical treatment was recommended to the patient, but the patient refused the treatment and therefore he was referred to physical therapy. In addition, the patient was evaluated by the neurology department two years ago with complaints of numbness and weakness in bilateral upper extremities, dizziness, involuntary dorsiflexion of the feet from the ankle after waking up in the morning, difficulty in maintaining balance while walking in the road from time to time and feeling like falling. It was understood that myelomalacia and os odontoideum and myelomalacia in the spinal cord persisted in the cervical MR images performed at that time (Figure 1). Current cervical MR images of the patient showed that the os odontoideum was separated from the C2 vertebra corpus compartment at the skull base (dystopic os odontoideum) and migrated 9.5 mm from the skull base towards the superior (bacillary invagination). In addition, the distance between the separated os odontoideum and the distal end of the clivus was narrowed. At this level, there was anterior compression of the medulla oblongata and proximal spinal cord and increased intensity due to this effect (myelomalacia). The anterior-posterior diameter of the proximal part of the spinal canal was 5.4 mm (Figure 1).

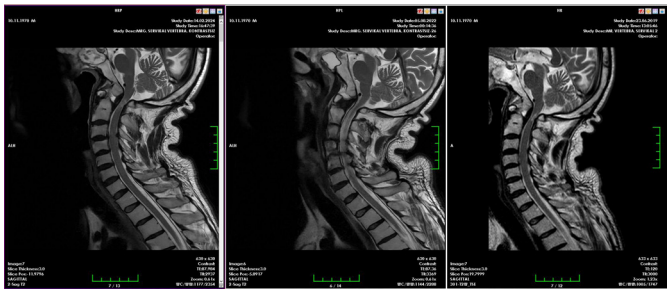

Figure 1. Cervical MR images from various dates showing os odontoideum, narrowing of the cervical canal, basilar invagination, and myelomalacia.

As the patient became symptomatic in the following period, to reveal cervical instability cervical computed tomography and cervical dynamic X-ray were performed to evaluate the bone structures and their mobility more clearly. Computed tomography showed that the dens fragment healed by adhering to the lower end of the clivus with possible apical ligament calcification after a possible odontoid dens fracture and narrowed the foramen magnum with parallel extension of the occipital bone (Figure 2).

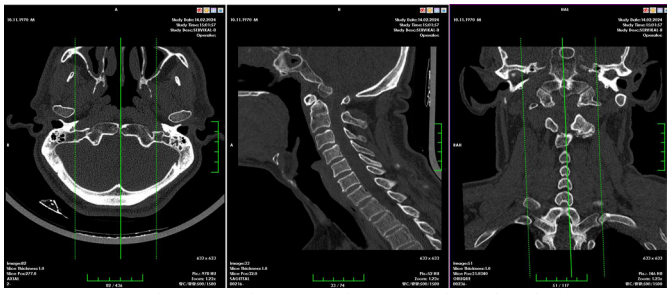

Figure 2. Cervical computed tomography images show that the dens fragment healed by adhering to the lower end of the clivus with possible apical ligament calcification after a possible odontoid dens fracture and narrowed the foramen magnum with the parallel extension of the occipital bone

When these radiologic images were compared with the old images, no additional pathologic findings were observed. However, cervical dynamic X-rays revealed that the patient had serious cervical instability (Figure 3).

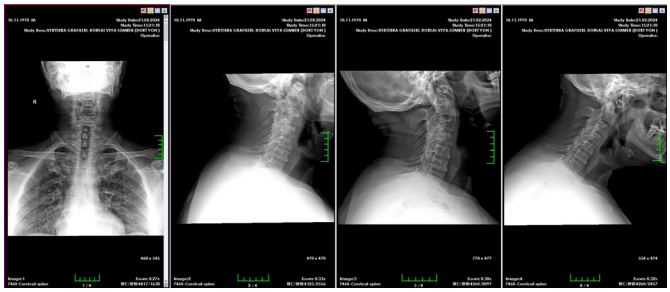

Figure 3. Cervical dynamic X-ray images show atlantoaxial instability.

For all these reasons, the patient was advised to undergo surgical treatment, but the patient refused the surgical intervention.

DISCUSSION

Today, two main theories are discussed for the formation of the os odontoideum: congenital and traumatic.[3] The congenital hypothesis argued incomplete fusion of the dens and axis vertebral bodies (segmental defects) due to developmental failure of the synchondrosis during embryonic development, non-traumatic osteonecrosis, congenital malformations (neurofibromatosis, skeletal dysplasias), autosomal dominant inheritance.[2] In the traumatic theory, it is argued that contraction of the alar ligament following an unrecognized odontoid fracture may lead to avascular necrosis and osseous remodeling contributing to ossicle formation. At the same time, deficiencies in arterial blood supply and trabecular bone at the base of the dens may predispose the dens to stress fractures caused by repeated microtrauma.[3,4] However, considering that os odontoideum is most commonly seen at the base of dens and not in synchondrosis, traumatic etiology has started to be accepted more than congenital etiology.[5] In our patient, there was no history of previous trauma or evidence of congenital malformation. However, considering the patient's age and the onset of symptoms in the last few years, it was thought that the os odontoideum may have a traumatic origin.

Common local symptoms of os odontoideum may include neck pain and stiffness, torticollis, ataxia, shoulder pain, headache, restricted neck movement, fatigue, hoarseness, respiratory dysfunction, swallowing difficulties, isolated occipital-cervical pain, upper extremity paresthesia including intermittent tingling and numbness in the upper limbs, lower extremity weakness, and gait disturbance.[6] In these patients, the os odontoideum may cause abnormal atlantoaxial instability (AAI) in both anterior and posterior directions. In these patients, compression of the vertebral artery and subsequent vascular complications may contribute to cervical myelopathy, along with spinal cord tension or bone compression. Myelopathic deficits can range from mild paresis or transient myelopathy to progressive tetraplegia, bulbar signs, and even death.[7] These patients may have central cord syndrome, hypoventilation syndrome (Ondine's

curse), Brown-Sequard syndrome, Lhermitte phenomenon, sleep apnea, lower cranial nerve dysfunction, hyperesthesia, bowel and bladder dysfunction, hypoesthesia, allodynia, hyperalgesia, vertebral artery occlusion and ischemia of the brainstem and posterior fossa structures can lead to seizures, cervical vertigo, syncope, visual disturbances, and in severe cases, sudden death. Late neurologic deterioration occurs in only 4% of patients.[2] In our patient, neurologic examination findings were normal except for a gradually increasing number of symptoms over the last few years. These symptoms included difficulty in performing fine manual skills such as buttoning buttons and pulling zippers, numbness in the hands, and the occasional sensation of stepping on a gap when walking.

The management of asymptomatic os odontoideum is controversial due to limitations in understanding its natural history. There are numerous studies in the literature showing that long-term conservative management is successful for patients with stable os odontoideum, as well as studies reporting cases of neurologic deterioration and sudden death. Non-surgical treatment methods for asymptomatic patients include serial imaging, longitudinal radiographic follow-up, and clinical observation. Immobilization consisting of a cervical collar or cervical traction may also be used.[8] It should be kept in mind that the initially stable os odontoideum may begin to develop AAI and associated symptoms. Patient education regarding the potential risks and avoidance of contact sports are also recommended.[9s] When os odontoideum was diagnosed in our patient, surgical treatment was primarily recommended to him five years ago. However, since the patient did not accept surgical treatment and neurologic examination findings were found to be normal, a conservative treatment option had to be applied. However, the patient's symptoms gradually increased in the following period and surgical treatment was recommended on his current admission again, but the patient refused this treatment again. The patient was obligatorily followed up again and the risks that might occur in the absence of surgical treatment were explained in detail again.

Sagittal spinal canal diameter <13 mm is strongly associated with myelopathy and studies report a 10% chance of developing this condition. Dystopic configurations of the os odontoideum and round morphology types are also risk factors for myelopathy and AAI. Surgical decompression and stabilization are recommended for patients with radiological indications of AAI, dynamic myelopathy, or neurological dysfunction. The most commonly used surgical treatment method is "posterior C1-C2 screw fixation and fusion". Other techniques include "sublaminar cabling of C1-C2" and "occipitocervical fusion". In addition, in recent years, "endoscopic endonasal resection techniques" have been applied more and more frequently in craniovertebral junction pathologies, including os odontoideum. It should not be forgotten that this approach should be considered as a complement, not an alternative, to the transoral-transnasal route, and that appropriate patient selection and surgical experience are important. Postoperative complications may include wound infection, cerebrospinal fluid leakage, persistent muscular neck pain, neurologic and vascular injury, anesthesia complications, pseudarthrosis, and hardware loosening.[8] A higher risk for perioperative complications has been reported in patients with unstable os odontoideum with cord compression or congenital ligamentous laxity.[10] In our patient, radiologic images showed myelomalacia findings for at least five years and the canal diameter was 5.4 mm at its narrowest point. However, since his previous symptoms were poor, neurological examination findings were found normal, and he refused the surgical intervention, he was initially treated conservatively. However, the progression of symptoms over time and dynamic radiographs performed to determine the cause of this progression revealed the development of AAI. Surgical treatment was recommended to the patient because of both the progressive symptoms increase and the presence of AAI, but, the patient did not accept the surgical treatment again.

CONCLUSION

In light of all these findings, it was argued that close and close follow-up of asymptomatic os odontoideum patients with conservative treatment may be appropriate considering the severity of complications of surgical treatments. On the other hand, it was suggested that the possibility of AAI should be considered in patients who become symptomatic.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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