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Research Article

Pathobiology of Migraine and its Putative Premonitory Signs-A Critical Commentary

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Abstract

Migraine is an episodic, recurrent neurological disease producing mild to severe headaches which affect humans of all ages. Before adolescent this disease occurs equally both in males and females. After menarche women are affected ~three times more than men which is mostly due to fluctuating hormone levels because of menstruation in females as men don't. Migraine evolution appears to be exclusively due to damage to the myelin sheath and neurodegeneration involving trigeminal nerve. The fluctuating sex hormones disturb the mineral homeostasis. Particularly, iron and copper which are transitional minerals and act as catalysts in metabolic processes that generate Free Radicals/ROS. Whenever ROS are produced in excess they overwhelm the body's antioxidant defense resulting in damage to myelin sheath, thus, exposing hypersensitive axons resulting in migraine pain. Similarly, other cranial nerves which are responsible for specific sensory and motor activities transmit special nerve impulses from the injured myelin/axon to higher centers which executes the specific response. Such responses manifest as visual, auditory, speech, allodynia, fatigue, nausea, vomiting and many more symptoms as PS. Hence, it is opined that PS have been erroneously attributed as part of migraine. Furthermore, the PS may occur in the absence of migraine and migraine does manifest many times in absence of putative PS. However, PS and migraine disease might have a common substrate for their etiology. Further investi-gations shall precisely clarify the situation. Moreover, the control measures in vogue are not rendering the desired results, hence, further studies on control measures with supplements are required for safety and effectiveness in controlling migraine disease. Hair mineral analysis is suggested to monitor the homeostasis of minerals which could help in definitive diagnosis of migraine and PS for devising specific control measures.

Keywords: Pathobiology; Putative Premonitory

Introduction

Migraine is the most common neurological disease which occur as frequent recurrent episodes of mild to severe headaches. Migraine affects all ages starting from childhood which particularly increases after adolescent, and then affects about three times more females than males, hence, there is typical sexual dimorphism (Singh., *et al*. 2019) [1]. Migraine is particularly perceived as a head pain that may vary from mild to an excruciating a pain. There occur other very scary premonitory signs which enhances the disability chances of migraine patients. In Migraine the throbbing and pulsating headache usually occur around temples on one side and very rarely on both sides. However, there are many more conditions/signs which sometimes may accompany migraine and are called 'Premonitory Signs' (PS). Migraine episodes accompanying PS are identified as 'Migraine with aura (25 - 30%) while the rest i.e., without PS are called Migraine without Aura. The aura which is recognized as a transient and reversible neurological disturbance and other non-painful symptoms deemed to be associated with migraine have not been clearly described/understood (Burstein., *et al*. 2015, Vetvik and MacGregor 2017, Chen and Wang 2018, Karsan and Goadsby 2018) [2-5].

The PS include visual changes-photophobia, hearing problems-phonophobia, smell defects-osmophobia, speech problems-aphasia, frequent urination, food cravings, nausea/vomiting, tiredness, weakness, forgetfulness, stiffness of neck with pain

and many more (Schulte., *et al*. 2015) [6]. Surprisingly these signs often vary with each migraine patient and even in different episodes in the same individual. Indeed most of these signs may not be a part of *migraine pain proper* and have been considered by many migraine experts as to be out of headache pain-the real migraine disease (Rossi., *et al*. 2005) [7]. Furthermore, their duration of occurrence varies enormously as they may disappear before the start of headache or they may even continue throughout the pain phase and even after the resolution of pain. Indeed many of these signs have also been observed in the absence of pain and even many migraine episodes does occur without PS (Goadsby., *et al*. 2017) [8]. Migraine with aura is more common in women than men possibly due to fluctuation of sex hormones (cause headaches which are not migraine) as women menstruate and men don't. Sex hormones interfere in the homeostasis of minerals, particularly, copper and iron and some others. Copper and iron ions produce free radicals resulting in oxidative stress (Dhillon., *et al*. 2011) [9]. Recent investigations have revealed that there appears to be a common denominator of migraine and PS which points towards "oxidative stress".

What is oxidative stress?

Oxygen is the life-line of biological tissues to generate energy as ATP. However, excess or less of a good thing could prove dangerous. During metabolic activities for production of energy in the mitochondria there is consumption of oxygen and glucose and free radicals are the bye products during this process. The tissues /organs which have very high metabolic activity generally produce more free radicals. Indeed free radicals are the oxygen containing molecules which have unpaired electrons in their outer orbit and are unstable. These molecules includes superoxide, hydroxyl anion, peroxynitrite, hydrogen peroxide, nitric oxide etc. These molecules (oxidants) in order to stabilize their structure react with other molecules and steal electrons to become stabilized. This reaction is called oxidation which destabilizes the molecules from which electron has been stolen. The process of oxidation could be beneficial or harmful. There are other molecules which can donate electrons without becoming free radicals are called Antioxidants. The most common antioxidants are enzymes as Super Oxide Dismutase (Cu, Zn-SOD), Glutathione peroxidase-Se, Glutathione Reductase-Se, Catalase, CoQ10, Vitamins -A, C, E, and others as Lipoic acid, Melatonin, HDL cholesterol, Flavonoids etc. When the balance is in favor of oxidants they cause **oxidative stress** and injure cell membranes and other molecules (Halliwell 2001, Gandhi and Abramov 2012) [10-11].

Oxidative stress is the imbalance between free radicals (Reactive Oxygen Species -ROS and Reactive Nitrogen Species-RNS) and antioxidants which are normally present in our body. Nervous tissue (brain) is highly active and consumes about 20% of the total oxygen inhaled, hence, produce free radicals in larger numbers. Moreover, nervous tissue is also most susceptible to free radical injury, due to their unsaturated fatty acid composition, thus, cause damage to myelin sheath, nerve cells and result in neurodegeneration. Recently, Free Radicals have been accepted mainly responsible for the development of various neurodegenerative diseases as Parkinson's Disease (PD), Alzheimer's Disease (AD), Amyotrophic Lateral Sclerosis (ALS),Multiple Sclerosis (MS), Migraine, Cancer and many more (Anderson., *et al*. 2014, Nunez and Hidalgo 2019, Ndayisaba., *et al*. 2019) [12-15]. As most of these diseases involve primarily the mitochondria for ATP production which have acquired errors in metabolism that often involve multiple systems with wide spectrum of manifestations which needs specific diagnosis for comprehensive control measures. Therefore, primarily this paper deals with migraine and its putative PS.

Mainly the fluctuations of sex hormones induce the imbalance of minerals particularly copper and iron. Both of these being transition minerals, when free, generate free radicals resulting in oxidative stress (Dhillon., *et al*. 2011, Ndayisaba., *et al*. 2019) [15,16]. The ROS's have been proposed to cause damage to myelin sheath covering axons of trigeminal nerves. The cell bodies of these afferents are located in trigeminal ganglion. Due to this damage there is establishment of "sterile inflammation" at the site of injury and there is release of CGRP as a body's defense mechanism.

Migraine appears to be exclusively a neurological disorder

The network of hypothalamus → hypophysis → endocrine glands → neurotransmitters → mineral homeostasis is so meticulously webbed that a slight aberration in it might result in several pathological problems including migraine (Alstadhaug 2009) [15]. The earlier " vascular theory" of migraine's cause as to be due to widening or contracting of blood vessels in the brain has become defunct (Goadsby 2009) [16]. Further, brain imaging by Magnetic Resonance Angiography have clearly demonstrated that "migraine headache is not associated with cerebral or meningeal vasodilation" (Schoonman., *et al*. 2008, Amin., *et al*. 2013) [17-18]. However, still most of the investigations into migraine attacks are mentioned to begin with prodromal signs capable of inciting nervous tissue which precede the start of headache pain. Recently, Burstein., *et al*.

(2015) [2]. also concluded that primarily there is involvement of hypothalamus, brain stem (trigeminal nerve ganglion) and cortex which induce transient neurological symptoms, preceding pain, that manifest as nausea, vomiting, sense of smell, abnormal sensitivity to light, noise, fatigue, muscle tenderness and many more. Considering all these signs it appears that migraine is not a simple headache but many parts of the nervous system are involved in its evolutionary process. Various parts of brain appear to be intricately implicated in the origin of migraine and so called its premonitory signs both of which might be comorbid ailments having a common denominator.

Brain parts involved in the evolution of migraine and premonitory signs

- **Brain Stem:** It contains vital centers which control heart and respiratory rate.
- **Cerebellum:** It controls balance and also coordinates body movement
- **Hypothalamus:** It regulates internal body processes and is called "Biological Clock" of the body
- **Pituitary Gland:** It produces hormones regulated by releasing factors produced by hypothalamus
- **Optic Nerve:** Supply and control the activity of the eye
- **Thalamus:** It controls the relay of sensory impulses from the peripheral nerves and spinal cord to specific areas in the cortex to sort out precisely for execution and manifestation.
- **Cerebrum:** It executes the higher intellectual functions and interprets the sensory impulses
- **Pineal Gland:** It produces melatonin involved in sleep/wake cycle and is a prodrug for scavenging free radicals
- **Choroid Plexus:** It produces cerebrospinal fluid which flows through the ventricles and other spaces in the nervous system.

Hypothalamus and its main functions

Hypothalamus → hypophysis → adrenal axis is the main controller of bodily functions and is vital for the overall homeostatic mechanisms throughout the body. Hardly any tissue/organ in the body escapes their influence. There are several nuclei in the Hypothalamus which are intricately involved in the expression of migraine and PS.

Nuclei of Hypothalamus

1. **Control of autonomic center (Dorsomedial hypothalamic nucleus) sympathetic and parasympathetic nervous systems):** Here it plays many vital roles as influencing blood pressure, heart rhythm, movement of digestive tract, respiratory rate and depth, size of the pupil of eye and other visceral functions.
2. **Control center for emotional and behavior (Medial preoptic nucleus):** These nuclei are involved in activities as sex drive, pleasures, emotions, fear, rage etc. Hypothalamus operates through autonomic nervous system as pounding of heart, high blood pressure, sweating and dry mouth.
3. **Regulation of body temperature: Hypothalamus (preoptic region):** Receives impulses from thermoreceptors located throughout the body and monitor temperature through flowing blood and regulates through cooling as sweating and heat retention through shivering to maintain constant temperature.
4. **Food intake regulation (ventro-medial nuclei):** As the levels of nutrients as glucose, amino acids or hormones (Insulin, Ghrelin, Leptin and others) vary hypothalamus regulates the feelings of hunger.
5. **Water and thirst balance regulation (thirst center):** Whenever concentration of body fluids become imbalanced osmoreceptors in hypotahalamus become activated and trigger the release of vasopression (ADH) from posterior pituitary to regulate water excretion through kidney. This influence also effects the frequency of urine as it occurs in migraine aura.
6. **Sleep-wake cycle regulation (Suprachiasmatic nucleus):** This is also called Circadian cycle and is a very complex phenomenon of sleep which is our biological clock and responds to daylight-darkness visual pathways. Melatonin production in pineal gland regulates sleep wake cycle and also act as a prodrug antioxidant.
7. **Functioning of endocrine glands and their regulation (Supraoptic and paraventricular nuclei) as stated below:**

   Hormone release

   The hypothalamus regulates, with great precision, various endocrine glands and organs through releasing

hormones (also called releasing factors) and the process is known as negative and /or positive feed- back mechanism. These hormones are stored and released as and when needed depending on various physiological/pathological stages.

Posterior pituitary

Hormone	Effect
Oxytocin	Uterine contraction
	Lactation (milk letdown reflex)
Vasopressin (antidiuretic hormone)	Controls water reabsorption and excretion through kidney and frequency of micturition.

Table 1

The hypothalamus is intricately involved in the modulation of a variety of fundamental physiological processes which include circadian cycle, appetite, thirst, micturition and some cardiovascular and endocrine systems. For such a wide variety of functions many peptide systems are involved which work synergistically. Therefore, any aberration in their role and disruption in homeostasis result in serious disruptions which cause many disease problems. Migraine is one such disease considered to be caused by fluctuating levels of hormones and their influence on disrupting homeostasis of several minerals as copper, iron, zinc, selenium, magnesium (Dhillon., *et al*. 2011) [9] and peptides as Orexins, Neuropeptide Y, Pituitary adenylate cyclase activating protein (PACAP), Oxytocin and some others (Strother., *et al*. 2018) [45]. The role of hypothalamus and these mineral and peptides in homeostasis is increasingly becoming prominent and much work is in progress to find newer control measures for migraine and its comorbidities. Though, the emphasis in most of the investigations into migraine pathophysiology and devising its control measures have mostly remained around head pain but now PS are also becoming critical targets.

Peptides that influence feeding behavior

Increase behavior	Decrease behavior
Ghrelin	Leptin
Galanin	Insulin
Neuropeptide Y	Cholecystokinin
	ACTH releasing factor
Orexin A, B	Insulin
Melanin-Concentrating hormone	Glucagon-like peptide

Table 2

Putative Premonitory signs of migraine and their origin

There are twelve pairs of cranial nerves (I-XII) originating from the ventral surface of the brain and on emerging out of it these nerves become part of the peripheral nervous system (cranial autonomic nervous system). The cranial nerves are named either according to the structure they supply or the primary function/s they perform. All these nerves are numbered using Roman numerals as I-XII starting from the frontal to the cephalic (posterior) region. Three nerves (I, II and VIII) are purely sensory, four nerves (IV, VI, XI, XII) convey motor signals away from the brain, while other five nerves (III, V, VII, IX, X) are mixed as having sensory and motor (sensorymotor) fibers.

All the cranial nerves perform specific motor and/or sensory functions for which each one of them has been specifically designated. These nerves are proprioceptors in nature and relay specific information to CNS about the tissues they innervate and balance of the body. All the cranial nerves are myelinated and metabolically very active which relay very fast sensory/motor nerve impulses for quick response. Due to higher metabolism there is production of increased ROS that generate oxidative stress in cranial nerves. Moreover, fatty nature of nervous tissue is very sensitive to oxidative stress and damage by ROS. The putative premonitory signs of migraine occur primarily due to damage to myelin sheath or neurodegeneration of any part of these sensory or motor cranial nerves. Injury to these tissues could be accidental or due to generation of "Free Radicals" also called Reactive Oxygen Species (ROS). Normally ROS as superoxide, peroxynitrite, nitric oxide, hydroxyl ion and hydrogen peroxide etc., are generated during metabolic activity for energy production and other mechanisms in the body. These oxidants play important physiological roles in triggering activities for immune systems and synthesis of proteins. Under normal conditions all the metabolic functions proceed in concert, however, whenever oxidants-ROS overwhelm antioxidants in the body (Vitamins A, C, E, CoQ10, SOD, Glutathione peroxidase, Zinc etc.) such imbalances result in oxidative stress which cause several pathological conditions as premonitory signs and migraine including many other neurological diseases (Kruit., *et al*. 2008, Inge., *et al*. 2017, Carrasco., *et al*. 2018) [19-21].

Along with recurrent episodes of migraines there may occur equally disabling non-headache symptoms which impacts patient's routine daily working activities and even quality of life. These symptoms include visual disturbances, gastrointestinal signs, allo-

dynia, restless leg syndrome, vertigo and vestibular- equilibrium problems, and many psychiatric problems (Chen and Wang 2018) [4] There are some more signs such as phono-phobia, cognitive disorders, anxiety, fatigue, neck pain or even more. Keeping in view the literature extant it was opined that the PS might be due to some aberrations to various sensory and/or motor cranial nerves. Recently, Migraine disease has most appropriately been found to involve ROS and trigeminal nerve-V for its evolution. However, PS also appear to have a common substrate with migraine as overwhelming Oxidative Stress by ROS against antioxidants of body's defense. Therefore, involvement of more cranial nerves, which supply head and neck region have been deemed to be the main source of developing putative PS.

Nerve	Function	Clinical Significance	Main Clinical Signs	Reference
Olfactory (I)	They are purely sensory having 6-7 million receptor cells in the nasal cavity and relays the information about smell. They arise from inside of the nose and connects directly with olfactory bulbs/centers in the brain	Patients are asked to sniff and identify different aromatic smells for clinical diagnosis. Lesions to this nerve results in partial or total loss of smell which presents quite variable signs.	• Osmophobia Anosmia, Hyposmia, Parosmia, Phantosmia and many more depending on the injury to olfactory cells. Many patients inform phantom smells of dead rats, garbage smell, burning rubber and some smells which are often nauseating, though such smells are not there.	[23]
Optic (II)	Fibers arise from retina of eye to form this nerve and pass through optic foramen. They are purely sensory and carry impulses for vision from retina to the brain	Oxidative stress causes Macular degeneration, Retinitis pigmentosa (RP), Autoimmune uveitis, cataract, Glaucoma, Diabetic retinopathy, corneal and conjunctival diseases etc. They present a wide spectrum of visual signs. Different visual fields are tested for determining the point of injury.	• Photophobia Dots, sparkles, stars, floaters, colored spots, flashing lights, tunnel Zig zag lines, vision, Blind spots, temporary blindness, scotomas, visual snow and many more depending on the damage to particular neuronal cells of the eye. "Alice in Wonderland Syndrome" appear as a classical, scary phenomenon of visual images from damaged tissues of the eye	[24,25.26,27]
Oculomotor(III)	Fibers of these nerves extend from ventral midbrain, purely motor supply eye muscles controlling their movements.	Eye reflexes tested with light, vision tested how eyes follow objects, size, shape, equality, rotation of eyes etc.	Ptosis (Drooping of eyelid), Double as well as distorted visions due to oxidative or other injury.	
Trochlear (IV)	Emerges from dorsal midbrain, enters orbits with Oculomotor nerve and control eye movements.	They are primarily motor and supply extrinsic and oblique muscles of the eye.	Trauma to these nerves results in double vision and reduced ability to rotate eye.	

Trigeminal (V) is the main nerve playing a pivotal role in the pathophysiology of migraine pain and is responsible for the laterality (due to its anatomical situation) of pain and related signs because it supplies the major parts of face and neck.	Largest of the cranial nerves which extend from pons to face and has three main branches which further divide into smaller branches: - 1.Opthalmic 2. Maxillary 3. Mandibular 1. Ophthalmic branch -Transmits sensory impulses from forehead, upper eyelids, nose, nasal cavity mucosa, cornea and lacrimal gland 2. Maxillary branch -Relays sensory impulses from nasal mucosa, palate, skin of cheek, upper teeth, upper lip and lower eyelids. 3. Mandibular branch-Mixed Impulses from interior tongue (but not taste buds), lower teeth, chin, temporal region of head. They also supply motor fibers for muscles of mastication and control the activity of eight muscles in this area. It includes four muscles of mastication and four others.	Inflammation of these nerves caused by ROS result in migraine disease that manifest as mild to excruciating unilateral throbbing pain. 1.OphthalmicV-1 Tested for corneal reflex by touching for blinking and other sensations, discharges from eye, nose etc. 2. MaxillaryV-2 Examined sensory impulses from nasal mucosa, upper teeth, palate, cheek skin, upper lip and lower eyelids. 3. MandibularV-3 Clinically patients are asked to crunch their teeth open mouth against resistance and movement of jaw from side to side.	The main nerve involved in the causation of migraine. The free radicals inflict injury to myelin sheath of axons of this nerve and the naked areas thus created appear as microscopic lesions. The exudates from such injury put mechanical pressure on the hypersensitive axons which manifest as migraine pain of varying intensities. • Touching of cornea with a wisp of cotton elicit blinking. There is lachrymal discharge and also from nasal cavity and cornea. • Tested for pain, touch and temperature sensations with a safety pin, hot and cold objects. • Any deviation in the movements of jaws or pain in teeth are recorded. Stiffness of neck is most probably due to injury to this branch which supply some of the eight muscles in the head/ neck region as muscles of mastication.	[28,29,30]
Abducent (VI)	Fibers of these nerves leave pons and reach the eye through the orbit. Mixed nerve, supplies the rectus and extrinsic muscle of the eye and conveys proprioceptive impulses from muscles to the brain.	Tested for nerve paralysis in which the eyes cannot move laterally and/or medially and other movements of eyes in co-ordination with III and IV nerves.	Trochlear-III, Oculomotor-IV and this nerve-VI function in collaboration with each other and control eye movements.	

Facial(VII)	Emerges from pons, enter temporal bone and supplies skin of the external ear, salivary and lacrimal glands, muscles used for facial expressions and relays sensory impulses from taste buds in anterior part of the tongue.	Anterior part of tongue is tested for ability of taste, sweet, salty, sour or bitter substances. Symmetry of face, closure of eyes, smile, whistle etc. Tearing from ammonia fumes is checked.	Paralysis of facial muscles, loss of sensation, rigidity. Dropping of lower eyelid, sagging of corner of mouth with difficulty in eating, dripping of tears etc. Bell's palsy recognized by paralysis of facial muscles on the injured side. Movements of eyebrows, wrinkles and many more complex movements of several muscles of the face during emotional, pleasure, rage and many more are also noticed.	[31]
Vestibulocochlear(VIII)	Fibers of these nerves arise from hearing and equilibrium apparatus which are located within the inner ear .These are purely sensory and have two divisions: Cochlear and Vestibular division that regulate hearing and equilibrium of the body.	Lesions in cochlear branch result in hearing problems and damage to vestibular division cause balance problems.	There is deafness, dizziness, rapid eye movement, loss of balance, nausea and vomiting, vertigo (subjective and objective). There are phantom sounds/ noises which manifest as tinnitus. Hearing is checked by using tuning fork. Assess gait for vertigo which can be peripheral (inner ear, vestibular nerve) or central (brain stem or brain).	[32, 33,34, 35, 36]
Glossopharyngeal(IX)	Motor fibers of these nerves are involved in swallowing and sensory fibers are involved in relaying taste, touch and heat from both tongue and pharynx.	They are checked for swallowing reflexes, patients are asked to cough and speak. Posterior part of tongue tested for taste.	Inflammation of these nerves impairs swallowing and taste particularly bitter and sour are seriously affected.	37,38,39
Vagus (X)	These nerves extend beyond head and neck region, emerge from medulla, and descends through neck region into thorax and abdomen. Fibers of these nerves are parasympathetic and are sensory and motor in function which regulate many vital bodily functions as heartbeat, breathing, abdominal organs and digestive system activity.	Since the fibers of these nerves supply laryngeal muscles, hence tested for voice and other systems like swallowing, impaired digestive system function. They also transmit sensory impulses from thoracic, and abdominal viscera, carotid sinus, carotid and aortic bodies for presso- , chemoreceptors, taste buds on posterior tongue.	Damage to this nerve makes life impossible as it supplies the vital organs like heart, lungs and abdominal viscera for the regulation of normal functioning of these organs. Any damage to these nerves produce symptoms of difficult y in swallowing and many other problems of digestive system. As all muscles of larynx ('Voice Box') are supplied by the branches of vagus, hence, paralysis of this nerve produces hoarseness or complete loss of voice.	[40]

Accessory (XI)	These are mixed nerves and emerge from lateral aspect of medulla, help movement of head and shoulder and also muscles of pharynx and larynx	Checked for sternocleidomastoid and trapezius muscles for strength by asking the patient to rotate head and shrug shoulders against resistance.	Injury to this nerve cause head turned towards injured side and shrugging of shoulders becomes difficult.	[41]
Hypoglossal (XII)	(*hypo*=beneath; *glossal*=tongue) These nerves supply mainly the tongue, are mixed nerves. Control speech, movements of intrinsic and extrinsic muscles, help mixing, chewing, swallowing and manipulating food.	Patients are asked to protrude and retract the tongue and any deviation in movement is noted. When only one side is affected, tongue deviates toward the affected side and begin to atrophy.	• APhasia Damage to these nerves produce difficulty in speech (aphasia) and swallowing and person cannot swallow and speak properly and babble. Difficulty in articulating words.	[42,43]

Table 3: Cranial nerves with their functions, clinical signs and diagnostic procedures.

All these cranial nerves are involved in sensory and/or motor activities of various organs they supply and very precisely control a wide spectrum of sensations of each organ in the head and neck region. Activities and control of various sensations usually involve hypothalamus, thalamus, pons, and various parts of head and neck, cerebral cortex. All these functionaries act in concert as long as the physiological norms are optimally maintained. However, during any imbalance particularly oxidative stress, physical injury or infection and compromised level of antioxidants, which results in very serious pathological conditions as PS. The PS as vertigo, equilibrium, smell, taste, eyesight, hearing, allodynia, nausea, vomiting, anorexia, depression, anxiety etc. may also be quite scary and disabling like migraine. However, the PS are usually comorbidities of migraine as the basic substrate for their cause is the same as "Oxidative Stress" due to ROS. There are specific nuclei in the hypothalamus and thalamus for processing these impulses primarily controlled by specific areas of cerebral cortex. Furthermore, premonitory signs do not always accompany the pain phase and may be present alone even in the absence of migraine (Chen and Wang2018) [22] Hence, premonitory signs are quite independent of migraine disease. The continual damaging of myelin sheath, a covering like our domestic electric wiring, and neurodegeneration are also routinely repaired to maintain proper nerve impulse transmission. The individual cranial nerve affected and the signs thereof are succinctly explained.

Olfactory- I

This nerve comprise of 6 - 10 million olfactory receptors having ciliated dendrites and cell bodies contained in specialized neuro-epithelium cells of higher recesses of nasal cavity. These cells are very unique in their capability of regeneration from stem cells after injury or senescent though it may not always be complete. Humans have about 400 types of odorant receptors on cilia of olfactory cells which are very specific as a given cell expresses only one type of odor. The incidence of smell disorders are ~1 - 2% which can seriously impact the routine life of the sufferers. Doty (2017) [23] a renowned scientist working in Smell and Taste Center, University of Pennsylvania, Philadelphia, USA, gave his personal views in his remarkable paper entitled "Olfactory dysfunction in neurodegenerative diseases: is there a common pathological substrate?" They have evolved a widely used test called "University of Pennsylvania Smell Identification Test (UPSIT). This test identifies a 40-odorant microencapsulated (scratch and sniff) test. This test has been translated into 30 languages and administered to over one million people all over the world. The results are assessed using a scale on the efficiency of the person to identify odors, detect, discriminate, recollect and assessment of the intensity as lowest of threshold of expression in comparison to blank. There are many more such odor identification tests developed globally and are available for olfactory performance. However, there is a wide spectrum of smell disturbances among different diseases which would vary in extent

of damage and nature of expression with individual person. Furthermore, an insight into smell disturbances might provide some crucial facts as to the pathobiology of migraine vis-a-vis premonitory signs of olfaction.

Optic nerve-II

Oxidative stress has been implicated in various diseases of the eye as it commonly comes with age, smoking, inflammation, light exposure, endoplasmic reticulum stress and many more factors which further enhances the degenerative changes in the tissues of the eye. Excessive production of ROS can bring about functional and morphological impairments in endothelial cells, retinal ganglion cells and retinal pigment epithelium (RPE).All these devastating cellular damages result in various eye problems which manifest in a wide spectrum of clinical signs (Oduntan and Mashige 2011, Masuda., *et al*. 2017, Kimura., *et al*. 2017, Benedetto and Contin 2019) [24-27].

Oculomotor-III; Trochlear-IV and Abducens-VI

All these three nerves needs to be considered together as they jointly work to control the eye movements. The movements of eye as vertical, horizontal, rotatory, obliquely etc. can be affected by any accidental injury or due to oxidative stress causing myelin damage and/or neurodegenerative diseases. There could be external strabismus in III, and internal strabismus in VI due to paralysis of these nerves. He., *et al.* (2015) [46] reported a case in a 64-year-old having typical visual aura without headache pain for ~30 years which was wrongly diagnosed as Transient Ischemic Attack (TIA). This patient had episodes of "homonymus blurred vision" or photopsia presenting many geometrical shapes as patchy, cord-like, zigzag, curtain-like and other irregular shapes.

Trigeminal-V

This is the largest nerve of all the cranial nerves and has three divisions which supply separately to muscles and other structures in head face and neck regions. This is the main nerve involved in the evolution of migraine along with some other signs depending on the extent of damage involving its different regions which are succinctly given in table-1. Trigeminal nerves play the major role in relaying sensory information of pain from face, head and intracranial structures as cerebral vasculature and meninges. The processing of these sensory impulses occur through the cell bodies of neurons in the trigeminal ganglia. This sensory information is then relayed to the dedicated brain stem areas and upper spinal cord regions and further processed by hypothalamus, thalamus and specific areas in cerebral cortex where the exact conscious perception of pain occurs which is the migraine proper in the real sense. Recently, functional imaging studies with positron emission tomography and fMRI showed that the real driver of the migraine attack might be involved in the connectivity of hypothalamo-brainstem. Furthermore, the prior stimulation of trigeminal nociception induced by ROS 24 hours before the pain onset appears to be mainly linked to migraine attack (Schulte and May 2016, Shatillo., *et al*. 2013, Denuelle., *et al*. 2007) [28-30]. However, it needs to be pointed out that PS do not appear in migraine without aura attacks, hence, they seem to be different entities and out of headache.

Facial- VII

It is a large mixed (sensory/.motor) nerve having five major branches: temporal, zygomatic, buccal, mandibular and cervical innervating the muscles of expression of face e.g., eyebrows, nostrils, lips for opening and closing eyes, mouth, smile etc. Oxidative stress has been found to cause various abnormalities in facial expressions which sometimes are also observed during migraine attacks. The most common among these is Bel's Palsy which is an acute mononeuropathy of unilateral paralysis of face. The disease has been named after a Scottish anatomist and surgeon Sir Charles Bell who first described it as a result of facial nerve dysfunction. The incidence of BP ranges from 60 - 75% of all the cases of unilateral facial paralysis. Terzi., *et al*. (2017) [31] investigated 32 patients (15 males and 17 females) of idiopathic BP and recorded serum total oxidant status, total antioxidant status and oxidative stress index. They concluded that oxidative stress was higher in BP patients as compared to controls and their data on oxidative stress is suggestive of basic etiology of BP.

Vestibulocochlear-VIII

These nerves are purely sensory and arise from hearing and equilibrium parts present in the internal ear which have two forms of fibers: afferent fibers for hearing receptors in cochlear division and efferent fibers for equilibrium in vestibular division. The two divisions merge to form this nerve-VIII. Migraine, dizziness, vertigo are quite common in general population as13%, 20 - 30%, 5 - 10%, respectively. However, the chance of combination of their occurrence could be expected up to 4% only. Similarly tinnitus which appears as subjective perception of varied noises though in the absence of any external stimulus. Causes of these maladies have not been fully understood as some migraine patients complain vestibular signs and some don't. There is some evidence that there could be no neuro-otologic abnormalities in common with migraine and dizziness (Calhoun., *et al*. 2011) [32] Recently, several studies have pointed out that oxidative stress has been an important factor in age-related hearing loss. Some studies on tinnitus, dizziness, buzzing ringing, hissing, beeping and many more signs which are generally subjective perceptions of individuals have been observed that reactive oxygen species (ROS) play pivotal roles in the etiology of

ontological and neurological diseases (Baguley., *et al*. 2013, Sema., *et al*. 2016) [33,34]. Recently, 'Vestibular migraine' and acute vertigo (Benign paroxysmal positional vertigo-BPPV) have been reported and most probable causes discussed for controlling these diseases (Li., *et al*. 2019, Kaski., *et al*. 2019) [35,36]. Many other signs as anxiety, depression, sleep problems, photophobia, phonophobia are also reported along with these signs. Such observations do indicate that there is a common substrate for many of these maladies and need further investigations.

Glassopharyngeal-IX and Vagus-X

These mixed nerves mediate many functions concerning upper aerodigestive tract. There is a very delicate and complex interplay between swallowing, breathing and communication which is regulated by sensory inputs and motor outputs of many cranial nerves. These processes are required to work precisely with perfection in concert as these nerves are in a very narrow anatomical region. Whenever there is any aberration in any one or both of these nerves it is manifest as signs of dysphasia, dyspnea, dysphonia or even more symptoms. These signs may be subtle or may be overlapping with some other diseases. Under such circumstances the diagnoses becomes confusing and problematic to devise appropriate control measures. Hence, otolaryngologists, Neurologists, and speech pathologists need to work together and nerve IX and X are tested simultaneously because both innervate throat and mouth (Erman., *et al*. 2009) [37]. Glossopharyngeal neuralgia is a disorder that is associated with repeated episodes of severe pain in the areas at the back of nose, tongue, throat, ear, voice box and tonsils. Episodes of pain may last from a few seconds to a few minutes and usually occur on one side of the face. The pain may be triggered by swallowing, speaking, laughing, chewing, or coughing. Glossopharyngeal neuralgia is thought to be caused by irritation of the glossopharyngeal nerve but the exact cause of the irritation is sometimes unknown (Shelat 2016) [38].

Symptoms of glossopharyngeal neuralgia typically occur in individuals over 40 or 50-year old. Pain usually begins at the back of the tongue or throat, and it sometimes spreads to ear or the back of the jaw. The pain can cause difficulty speaking and swallowing. In rare cases, the disorder can cause a slow heart rate (bradycardia), hypotension, no heart beat due to cardiac arrest (asystole), or fainting (Krasoudakis., *et al*. 2015) [39].

Patients having dysfunction with vagus nerve show dysphagia, hoarseness and dyspnea which usually depend on the site of the lesion. Most of the time both the nerves may be affected and signs usually depend on the anatomical proximity. History of the patient is most important for the clinician as to the course of the ailment, however, specific changes in voice are very crucial to discern laryngeal pathology (Sataloff., *et al*. 2005) [40].

Spinal accessory-CN XI

SAN has two components as spinal and cranial. Cranial part supplies pharyngeal and laryngeal muscles and soft palate along the vagus nerve. Spinal part extends from C1 - C5 and innervate motor fibers of trapezius and sternocleidomastoid muscles which help move the head and neck and conveys proprioceptor impulses to these muscles. CN XI palsy is the most commonly occurring sign in injuries to this nerve. Such injuries usually occur during surgery in the posterior triangle of the neck or during lymph node biopsy (Kelley., *et al*. 2008) [41]. Patients show dropped shoulder, limited arm abduction, pain and increased prominence of scapula. Contraction of these muscles give rise to a condition called torticollis or wry neck.

Hypoglossal –XII

These nerves play an important role swallowing and speech. This pair innervates the muscles of tongue and control its movements during speech, manipulation of food and swallowing. They also direct voluntary movements of tongue and involuntary functions as clearing of saliva and food by swallowing. The nerves also are involved in adjusting the tongue movements for learning desired sounds (Walker 1990) [42]. Other important functions are as protruding, retracting, depressing the tongue also for changing the shape of tongue (Lin and Barkhaus 2009) [43].

Indeed all the last four pairs of nerves which are called Lower Cranial Nerves (LCN) function precisely and rarely affections of them are isolated but majority of them show cases of multiple nerve involvement. The LCN may show lesions of vascular, traumatic, iatrogenic, nutritional, metabolic, immunologic, genetic, degenerative and or neoplastic origin. Hence, the lesions and symptoms, thus, developed need to be examined clinically by different specializations for specific diagnosis and devising proper control measures (Finsterer and Grisold 2015) [44,45].

Conclusions

Migraine appears to be exclusively a neurological disease involving trigeminal cranial nerve-V. The mechanisms involved are probably the ROS (Free Radicals) causing oxidative stress and damage to myelin sheath of this nerve. The damage inflicted by ROS

transmits sensory impulses to higher centers as hypothalamus, thalamus and specific areas of cerebral cortex where actual perception occurs and executed. The putative Premonitory signs (PS) are similarly processed by the other cranial nerves which perceive the motor or sensory impulses and conveys to marked areas of cortex for monitoring the responses. There is common substrate for both migraine disease and PS which is primarily oxidative stress exerted by ROS produced due to imbalance of overwhelming oxidants against antioxidant defense system of the body. Recent investigations deal PS as separate disease entities and studies are underway to find out specific control measures for migraine and PS as comorbidities.

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