

Novel and Conventional Causes of Trigeminal neuralgia

Mahmoud Abdel-Moety Monzer¹ and Abdel-Salam El Ashry²

¹Department of Neurology, Faculty of Medicine (For Boys), Al Azhar University, Cairo, Egypt

²Department of Radiology, Faculty of Medicine (For Boys), Al Azhar University, Cairo, Egypt
mahmoudabdelmoety@yahoo.com

Abstract: Background: Trigeminal neuralgia (TN) is the most excruciating pain known to humanity and considered one of the most painful afflictions known in medical practice. There are two main types: typical or “classic” form and atypical form of trigeminal neuralgia. **The aim of this study:** The aim is identification if there are new etiology for trigeminal neuralgia. This will help to reach more accurate diagnosis and may contribute to more effective treatment. **Subject and methods:** All patients were submitted to detailed history, clinical examination and neuroimaging as CT and / or, MRI + MRA brain. Laboratory investigations, carotid and vertebralbasilar duplex, ECG, Echocardiography, Nerve conduction study and different modalities of Evoked Potential were done for patients according to etiology and when indicated. **Results:** This study was carried out on 73 patients with trigeminal neuralgia. It affects females more than males. In the vast majority of cases (91.8%) pain is limited to one side of the face, however right side (53.4%) more affected than left side (38.4%). Occasionally it affects both sides of the face in 8.2 % of cases at different times in an individual, or even more rarely at the same time (called bilateral TN). Pain involve three divisions of the face in 86.3 % of cases, lower part of the face in 9.6 % of cases and upper part of the face in 4.1 % of cases. 95.2 % of patients have typical or “classic” form of trigeminal neuralgia TN1. TN2 is present in 7 % of cases. Regarding etiological factors for symptomatic trigeminal neuralgia in this study; trigeminal hypoesthesia is present in 14 % of cases, hearing affection is present in 7 % of cases, pyramidal signs are present in 12.6 % of cases and long sensory tract affection is present in 7 % of cases. Normal MRI & MRA Brain is present in 39.2 %. Normal MRI with attenuated one or both vertebral arteries in MRA Brain is present in 12.6 % of cases. Also, this study found that stroke etiology present in 43.8 % of cases and rare in people under the age of 40 (7 %) of cases but migraine is not rare (12.6 %) of cases. 4.2 % of cases has space occupying lesions aged 31- 48 years. 4.2 % of cases has polyneuropathy aged 23-32 years. Also, one case (1.4 %) has multiple sclerosis. Pain after oral surgery o physiotherapy for Bell’s palsy is present in (2.8 %) for each. Hypertension, diabetes mellitus (DM), and dyslipidemia were risk factors for strokes. **Conclusion:** Detailed history, clinical examination, and neuroimaging as MRI ± MRA brain are essential to know etiology, diagnosis with subsequent effective treatment for patient with trigeminal neuralgia. Attenuated one or both vertebral arteries, stroke, migraine, space occupying lesions, polyneuropathy, multiple sclerosis, oral surgery or Bell’s palsy and it’s physiotherapy are etiological factors for symptomatic trigeminal neuralgia.

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1. Introduction

Trigeminal neuralgia (TN or tic douloureux) is a disorder of the fifth cranial (trigeminal) nerve one of the largest nerves in the head. It usually occurs in sudden short attacks lasting from a few seconds to about two minutes, which stop abruptly. Over time attacks become longer, more frequent of intense pain. A series of attacks can last days, weeks, or months then subsides. In some cases, the condition becomes progressive and pain is always present. It’s possible for the pain to improve or even disappear altogether for several months or years at a time (known as a period of remission), although these periods of remission tend to get shorter with time. The typical or “classic” form of the disorder type 1 (TN1) caused by irritation of the trigeminal nerve. The typical form (TN1) causes episodes of sporadic sudden extreme facial pain described as intense stabbing, shock, sharp, shooting, or electric shock-

like pain in the areas of the face where the branches of the nerve are distributed. Atypical form of the disorder called TN2 is characterized by constant aching, burning, stabbing pain of lower intensity than TN1. The typical or “classic” form and TN2 may occur in the same person, sometimes at the same time (*Bethesda, 2013* and *Phoenix, 2017*).

Pain can be triggered by routine acts such as vibration, touching the skin lightly, washing, brushing teeth, shaving, applying makeup, touching face, blowing the nose, speaking, smiling, breeze air conditioning on face, washing with cold water, eating, drinking hot or cold beverages. Pain can occur without any trigger whatsoever. In severe cases, attacks may occur hundreds of times a day. More than one nerve branch can be affected by the disorder (*Phoenix, 2017*).

The trigeminal vessels, which varied between two and five in number, arise from two or three of

the following arteries: the superolateral pontine (92%) perfuse the motor root and most of ophthalmic part. anterior inferior cerebellar (AICA) (88%), inferolateral pontine (72%), and superior cerebellar (SCA) (12%). The trigeminal vascular twigs had a mean diameter of 0.215 mm. Maxillary part was most often irrigated by inferolateral and posterolateral pontine. Anterior inferior cerebellar (AICA) irrigate mandibular part. Also, superior cerebellar, basilar and trigeminocerebellar share in their irrigation (*Cetković et al., 2011*).

Aim of the Work:

The aim of this work is to identify etiology and if there are new causes for trigeminal neuralgia in a trial to help us to reach more accurate diagnosis. This may help to choose effective treatment accordingly.

2. Patients and Methods:

This retrospective study was carried out on 73 patients with trigeminal neuralgia. This study was carried out at the neurology department of Hay El-Gama hospital from December 2014 to December 2016.

All patients were submitted to:

1-Detailed medical and neurological history.

2-General medical examination.

3-Neurovascular examination.

4-Neuro-imaging:

A-MRI ± MRA brain was done for all patients except 2 patients has MRI phobia so C.T brain was done for them.

B-B-Duplex:

All patients with stroke were subjected to B mode-colored duplex sonography of both carotid and vertebralbasilar arteries.

5-Echocardiography: were done for all patients with stroke.

6-ECG done for all patients with stroke and when indicated.

7-Laboratory investigations: including complete blood count (CBC), ESR, fasting blood sugar (FBS), 2 hours post prandial blood sugar (PPBS), liver and kidney function tests, lipid profile and serum uric acid were done according to etiology and when indicated. ANA, ANCA, anti-DNA, protein C, S and anticardiolipin antibodies, were done for patients younger than 40 years and patients without obvious risk factors for stroke and when indicated.

8-Neurophysiological assessment:

1-Nerve conduction study (NCS) was done for patients with polyneuropathy.

2-Visual Evoked Potential (VEP), Brain Stem Auditory Evoked Potential BAEP, Somatosensory Evoked Potential (SSEP), and Somatosensory Trigeminal Evoked Potential were done for 2 cases one of them has multiple sclerosis and other has vasculitis.

9-Statistical analysis:

The data were analyzed using statistical program for social science (SPSS) version 20.0 to obtain; descriptive data (Mean, standard deviation) & analytical statistics (student "t" test, chi square, Pearson correlation coefficient r and one-way analysis of variance {ANOVA}). (*P* value less than 0.05 is considered significant and 0.01 as highly significant).

3. Results:

This study was carried out on 73 patients with trigeminal neuralgia. Trigeminal neuralgia affects females {39 cases (53.4 %)} more than males {34 cases (46.6 %)}. In the vast majority of cases {67 cases (91.8%)} pain is limited to one side of the face, however right side more affected than left side {39, and 28 cases (53.4, and 38.4%)}. Occasionally it affects both sides of the face in 6 cases (8.2 %) at different times in an individual, or even more rarely at the same time (called bilateral TN). Pain involve three divisions of the face in 63 cases (86.3 %), lower part of the face in 7 cases (9.6 %) and upper part of the face in 3 cases (4.1 %). Vast majority of cases of this study (68 patients {95.2 %}) have typical or "classic" form of the disorder trigeminal neuralgia type 1 (called TN1). The "atypical" form of the disorder called trigeminal neuralgia type 2 (TN2) is present in 5 cases (7 %); 3 of them has ischemic stroke 2 of them have pontin infarction. Both forms of pain may occur in the same person, sometimes at the same time. In this study, this is present in one patient (1.4 %) has attenuated one of vertebral arteries in MRA Brain other had oral surgery (1.4 %).

Regarding etiological factors for symptomatic trigeminal neuralgia in this study; trigeminal hypoesthesia is present in 10 cases (14 %) all of them has vascular etiology; 8 cases have ischemic stroke and 2 cases have attenuated one of vertebral arteries in MRA Brain. All three divisions of one side of the face are involved in 6 cases (8.4 %), 5 cases of them (7 %) have hemihypoesthesia. Lower part of the face is involved in 3 cases (4.2 %) followed by upper part of the face one cases (1.4 %).

Hearing affection is present in 5 cases (7 %); 4 have ischemic stroke and one of them has space occupying lesion.

Facial spasm is present in one case (1.4 %) has ischemic stroke.

Pyramidal signs are present in 9 cases (12.6 %) all of them have ischemic stroke.

7 patients (9.6 %) were hypertensive also 7 (9.6 %) have diabetes mellitus. They have single, or multiple ischemic stroke and 2 of them have attenuated vertebral vessels. Migraine was found in 9 cases (12.6 %); 5 of them have ischemic strokes, and 5 have attenuated vertebral vessels.

In this study 32 cases (43.8 %) have stroke. Stroke is not rare in people under the age of 40 {5 cases (7 %)}. Deep parietal is the commonest site of

infarction {19 cases (43.8 %)} then capsular {5 cases (7 %)}, followed by thalamic, pontin, parietal {two cases (2.8 %) for each} and lastly lateral medullary and complete MCA occlusion {one case (1.4 %) for each} in patients of this study.

Space occupying lesions (SOL) are seen in patients between ages of 31 and 48 {3 cases (4.2 %)}. One of them is 40 years' male has

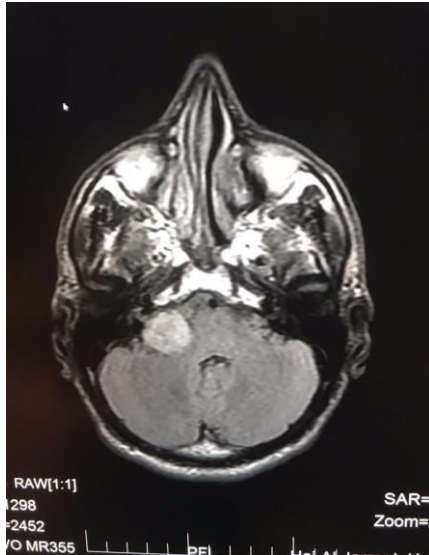


Figure 1

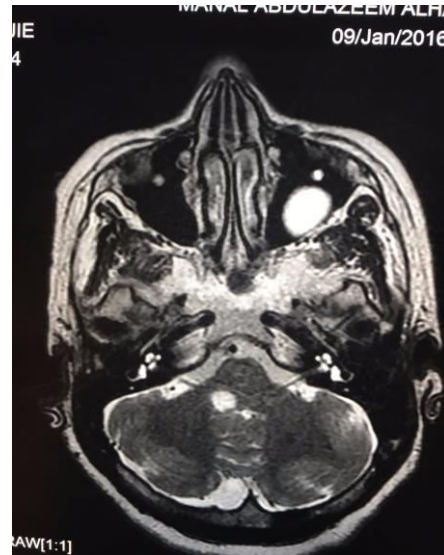


Figure 2

cerebellopontin angle schwannoma (Figure1), other female aged 31 years has recurrent cerebellopontin angle schwannoma, and other 48 years' female has inferior peduncular cystic lesion (Figure 2). On other hand 2 patients with ischemic stroke accidentally discovered to have a symptomatic meningiomas not related for trigeminal neuralgia.

Polyneuropathy (PN) is seen in patient between ages of 23 and 32 {3 cases (4.2 %)} all of them have axonal changes in nerve conduction study, normal laboratory work, and MRI & MRA Brain. One of them is 25 years' male has left trigeminal neuralgia and long standing (PN) after infection during childhood period with wasting in tibialis anterior muscle. 2nd one is 32 years' male has eczema, left trigeminal neuralgia, right ulnar and femoral neuropathy. Other one of them was 23 years' female has right trigeminal neuralgia, short stature, paraparesis due to kyphoscoliosis in MRI dorsal region, normal MRI & MRA Brain but with 1st degree Arnold Chiary malformation.

Trigeminal pains after oral surgery is present in 2 cases (2.8 %) have normal MRI & MRA Brain one of them has mandibular hypoesthesia not recovered for 6 months. Other patient has severe pain for years and was resistant to multiple neuropathic pain killers.

Right trigeminal pain after physiotherapy for Bell's palsy is present in 2 cases (2.8 %) recovered after stoppage of electric stimulation for one week followed by decrease number of sessions to 2 sessions per week until recovery.

Trigeminal pain after psychological stress is present in one case (1.4 %) has normal MRI & MRA Brain

Regarding laboratory finding in this work, elevated ESR level was found in 3 patients (4.2 %) 2 of them have ischemic strokes. Dyslipidemia was

found in 2 patients (2.8 %) both have ischemic strokes.

Elevated level of anti-cardiolipin, and ANA were found in one patient has history of arthritis, 2 abortions, multiple lacunar infarcts, axonal changes in nerve conduction study, Visual Evoked Potential, Brain Stem Auditory Evoked Potential, Somatosensory Evoked Potential, and Somatosensory Trigeminal Evoked Potential.

Normal MRI & MRA Brain is common in younger people (age ranged between) 28 cases (39.2 %) 3 of them have polyneuropathy. Also, there is 28 years female patient has multiple sclerosis (1.4 %) proved by Evoked Potential modalities.

From history taking, general, neurological examination, CT scan or MRI & MRA Brain findings the patients are classified in this study into 5 groups:

Group (I) include 25 patients (35 %) their ages ranged between 18 – 56 ± 33.9 years with a mean 33.88 ± 9.5 year have normal MRI & MRA Brain.

Group (II) includes 9 cases (12.6 %) aged 38.3 ± 14.2 years with normal MRI and attenuated one or both vertebral arteries in MRA Brain.

Group (III) includes 32 cases (43.8 %); 5 cases of them (7 %) under age of 40. 23 (31.5 %) case have multiple infarcts aged (54 ± 18), and 9 cases (12.6 %) have single ischemic stroke aged (47.56 ± 5). 3 of patients with stroke have attenuated one of the vertebral arteries in MRA Brain. One of them is a 28 years' female has bilateral trigeminal pain with multiple lacunar infarcts, markedly

attenuated right vertebral artery and dominant left one (Figure 3). Other one 47 years' male has trigeminal pain, lower division hypoesthesia with

high parietal infarction, hypoplastic left vertebral artery (Figure 4).



Figure 3



Figure 4

Group (IV) includes 3 cases (4.2 %) have space occupying lesions (SOL) aged 39.67 ± 8.5 .

Group (V) includes 3 cases (4.2 %) have polyneuropathy (PN) aged 26.67 ± 4.7 have normal MRI & MRA Brain with axonal changes in nerve conduction study.

Nerve conduction study (NCS) was done for all patients with polyneuropathy and showed axonal changes in all patient.

Visual Evoked Potential (VEP), Brain Stem Auditory Evoked Potential BAEP, Somatosensory Evoked Potential (SSEP), and Somatosensory Trigeminal Evoked Potential were done for 2 cases one of them has demyelinating pathology going with multiple sclerosis and other has axonal changes going with vasculitis.

Table (1): Comparison between groups according to demographic & clinical data:

		Normal MRI & MRA Brain Group	Normal MRI Brain and Attenuated VA group	Stroke Group			SOL Group	PN Group	P value	Statistical significance
				Single stroke	Multiple strokes	Stroke with attenuated VA				
Number of patients		25 (34.2 %)	9 (12.3 %)	9 (12.3 %)	20 (27.39%)	3 (4.1 %)	3 (4.1 %)			
Age		33.88 ± 9.5	38.33 ± 14.3	47.56 ± 5	54.14 ± 18	45.33 ± 4.6	39.67 ± 8.5	26.67 ± 4.7	<0.001	Significant
Sex	Female 39 (53.4%)	17 (68 %)	5 (55.6 %)	2 (22.2 %)	11 (55 %)	0	2 (66.7%)	1 (33.3)	0.128	Not significant
	Male 34 (46.6%)	8 (32 %)	4 (44.4%)	7 (77.8 %)	9 (45 %)	3 (100 %)	1 (33.3)	2 (66.7%)		
Side	Left 28 (38.4%)	13 (52 %)	3 (33.3 %)	3 (33.3%)	5 (25 %)	0	2 (66.7%)	2 (66.7%)	0.647	Not significant
	Right 39 (53.4%)	11 (44.0%)	4 (44.4%)	6 (66.7%)	13 (65 %)	3 (100 %)	1 (33.3)	1 (33.3)		
	Bilateral 6 (8.2%)	1 (4.0%)	2 (22%)	0	2 (10 %)	0	0	0		
Division	All 63 (86.3%)	22 (88.0%)	7 (77 %)	6 (66.7%)	18 (90 %)	3 (100 %)	3 (100 %)	3 (100 %)	0.676	Not significant
	Lower 7 (9.6%)	2 (8.0%)	1 (11 %)	3 (33.3%)	1 (5 %)	0	0	0		
	Upper 3 (4.1%)	1 (4.0 %)	1 (11 %)	0	1 (5 %)	0	0	0		
Hypertension 7 (9.8 %)		0	0	4 (44 %)	1 (4.8%)	2 (66.7%)	0	0	<0.001	Significant
Diabetes mellitus 7 (9.8 %)		0	0	4 (44 %)	1 (4.8%)	2 (66.7%)	0	0	<0.001	Significant
Headache 9 (12.6 %)		1 (4 %)	3 (33.3%)	2 (22 %)	1 (4.8%)	2 (66.7%)	0	0	0.013	Significant

Magnetic Resonance Imaging & Angiography Brain (MRI & MRA Brain). Space occupying lesions (SOL). Polyneuropathy (PN). Vertebral artery (VA).

4. Discussion

Trigeminal neuralgia (TN) is usually a long-term condition. It is most common cause of neuralgic pain in the face, with an incidence of 3-5 cases per 100 000 people (*Green 2007* and *Phoenix, 2017*).

Trigeminal neuralgia diagnosis is based primarily on medical history including type and location of pain in various parts of the face and factors that trigger the pain. Physical examination and thorough neurological examination with special stress to determine which part of the trigeminal nerve is being affected by examination of motor and different modalities of sensation. Because of overlapping symptoms and the large number of conditions that can cause facial pain, obtaining a correct diagnosis is difficult, but finding the cause of the pain is important as the treatments for different types of pain may differ. Also, patient list any diseases being treated for and any facial injuries, surgeries, or procedures that have been performed on his or her face. Then they will order tests to rule out other conditions with similar symptoms, such as cluster headaches, short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), post herpetic neuralgia, septic tooth, temporomandibular joint disorders and sinusitis (*Zakrzewska, Joanna 2002* and *Yugraka and Chou 2016*).

Trigeminal neuralgia has a significant impact on a person's quality of life, resulting problems such as avoidance of social contact and daily activities such as eating and talking because they fear an attack so patient has weight loss, isolation, depression and sleep disturbance that may render individuals more vulnerable to pain and suffering. Many lose their jobs, marriages because of the debilitating nature of the pain. Thus, there are individual, family, and societal costs of TN (*Tolle et al., 2006* and *Koopman et al., 2009*).

In this study, trigeminal neuralgia affects females (53.4 %) more than males (46.6 %) this go with same line with *Gronseth et al. (2008)* and *Yugraka and Chou (2016)* who found that condition affects women more often than men. If trigeminal neuralgia occurs in younger people this rise concern for potential structural cause; normal MRI with attenuated one or both vertebral arteries in MRA Brain is present in 12.6 % of cases aged 38.3 ± 14.2 years. Also, this study found that patients with MS, brain tumor, polyneuropathy and 7 % of cases aged 40 having stroke etiology this agree with report of *Flemming (2013)*.

In the vast majority of cases pain is limited to one side of the face 67 cases (91.8%). Pain involve three divisions of the face in 63 cases (86.3 %), lower part of the face in 7 cases (9.6 %) followed by upper part of the face 3 cases (4.1 %). The right side

is more frequently involved more than left side {39 & 28 (53.4 & 38.4%) by same sequence} this go with finding of *Maarbjerg et al. (2014)*. Occasionally it affects both sides of the face 6 cases (8.2 %) at different times in an individual, or even more rarely at the same time (called bilateral TN), this near to report of *Gronseth et al. (2008)*.

The initial diagnostic evaluation of a patient with TN naturally focuses on those clinical characteristics known to identify patients with symptomatic trigeminal neuralgia (STN). The characteristics include the presence of trigeminal sensory deficits and/or bilateral involvement. In this study, trigeminal hypoesthesia is present in 10 cases (14 %) all of them has vascular etiology; 8 cases have ischemic stroke and 2 cases have attenuated one of vertebral arteries in MRA Brain. All three divisions of one side of the face are involved in 6 cases (8.4 %), 5 cases of them (7 %) have hemihypoesthesia. Lower part of the face is involved in 3 cases (4.2 %) followed by upper part of the face one cases (1.4 %).

Vast majority of cases of this study (68 patients {95.2 %}) have typical or "classic" form of the disorder trigeminal neuralgia type 1 (called TN1). The "atypical" form of the disorder called trigeminal neuralgia type 2 (TN2) is present in 5 cases (7 %); 3 of them has ischemic stroke 2 of them have pontine infarction. Both forms of pain may occur in the same person, sometimes at the same time. In this study, this is present in one patient (1.4 %) has attenuated one of vertebral arteries in MRA Brain other had oral surgery (1.4 %).

Hearing affection is present in 5 cases (7 %); 4 have ischemic stroke and one of them has space occupying lesion.

Facial spasm is present in one case (1.4 %) has ischemic stroke.

Pyramidal signs are present in 9 cases (12.6 %) all of them have ischemic stroke.

7 patients (9.8 %) were hypertensive also 7 (9.8 %) have diabetes mellitus. All of them have single, or multiple ischemic stroke and 2 of them have attenuated vertebral vessels. This agree with *Sotir et al., (2005)* and *Pinto et al., (2006)* they found that hypertension is much more common in lacunar strokes than non-lacunar strokes. Also agree with *Adria et al., (2005)* who found that DM is specific risk factor for ischemic stroke and *Arboix et al., (2007)* who found that hypertension and diabetes mellitus was specific predictor of recurrent lacunar strokes.

Pain in the face is almost never the only sign of a stroke. Head pain can be a sign of stroke, but even when headaches are a signal of a stroke, the headaches are accompanied by other neurological problems. In this study 32 cases (43.8 %) have stroke. Stroke is not rare in people under the age of 40 {5 cases (7 %)}. Deep parietal is the common site of infarction {19 cases (43.8 %)} then capsular {5

cases (7 %)), followed by thalamic, pontin, partial {two cases (2.8 %) for each} and lastly lateral medullary and complete MCA occlusion {one case (1.4 %) for each} in patients of this study.

Symptomatic trigeminal neuralgia due to stroke in brainstem infarction is said to be rare. Facial pain related to pontine and Wallenberg's syndrome may be either persistent, and occasionally occurs in brief attacks. Here, there is 2 cases with pontin and one patient with a left lateral medullary infarction who started having first trigeminal neuralgia after stroke. Ischemic lesions at the root entry zone (REZ) at the pontin level or trigeminal spinal tract and nucleus at the lower levels of the medulla seem to be involved in the pathogenesis of the pain. The pain paroxysms were suppressed with gabapentin and anti-ischemic in those patients and this agree with findings of (*Pizza et al., 2010* and *Carlos Ordás et al., 2011*). The generator of pain in other cases is in the central nervous system but central sensitization. Equally, continuous pain in the atypical form can result from the progressive damage to the central terminals of trigeminal afferents, which become the source of continuous ectopic discharges (*Seth Love and Hugh Coakham, 2001*). On the other hand, relationship between trigeminal neuropathic pains, and stroke are very limited in the current study. However, there is only one clinical epidemiological study showing that TN might be a risk factor for stroke. However, the increased risks of stroke are concentrated in 60-65 years group of age. This increase in risks might be associated with age-related vascular changes (*Pan et al., 2011*). The mechanism underlying the influences of TN on stroke has not been reported. However, *Wei Wang et al., (2015)* found that trigeminal neuropathic pain may increase the mean arterial pressure and the content of calcitonin gene-related peptide in the plasma of rats, thus increasing the cerebral blood flow in the frontal cortex of the ET-1 focal cerebral ischemia-reperfusion model. Also study of *Eikermann-Haerter et al (2012)* on a murine model of familial hemiplegic migraine (FHM) revealed that FHM may increase stroke vulnerability by facilitating ischemic depolarizations.

Migraine was known as unidentified risk factor for trigeminal neuralgia; *Alex Mauskop (2011)* suggested that disturbance in trigeminal neuralgia is localized to the nerve itself after it exits the brain, while migraine originates in the brain and then involves fibers of the trigeminal nerve. There have been a few reports of migraine-tic where patients have both the electric shock-like sensation and persistent headache with nausea and other migraine symptoms. Paroxysmal hemicrania and cluster headaches are sometimes misdiagnosed as trigeminal neuralgia because those two condition often cause excruciating pain around the eye. On the other hand, in this study migraine was found in 9 cases (12.6 %); 5 of them have ischemic strokes, 5

have attenuated vertebral vessels. This go with the same line with *Teri Robert and Krusz, (2007)* and *Kuan-Hsiang et al., (2015)* who found that trigeminal neuralgia and migraines can coexist and certainly migraines can be strongly familial, the association between these conditions suggests a linked underlying mechanism. Also, trigeminal nerve nuclei and the brainstem are involved in processing of painful signals arriving there and single medication can help both clinical situations. Also, botulinum toxin success with Migraines, trigeminal neuralgia, temporomandibular dysfunction, and other facial pain. On same line *Pichiecchio et al., (2002)* and *Drummond et al., (2006)* present a 32-year-old woman with Parry-Romberg syndrome or progressive facial pain and hemiatrophy (PFH), migraine and an intracranial aneurysm. This rare disease characterized by atrophy of the skin and subcutaneous tissue on one side of the face. These findings support the hypothesis that the disease could be related to a neural crest migration disorder, from which both fronto-nasal mass and cranial vessels take origin. Also agree with the same line with *Larry et al., (2006)* who found that migraine is a risk factor for stroke especially in young women.

Compression of the trigeminal nerve by ectatic vessels, a known cause of idiopathic trigeminal neuralgia which was not found in this study. However, space occupying lesions (SOL) were found in patients between ages of 31 and 48 {3 cases (4.2 %)}. One of them is 40 years' male has cerebellopontine angle schwannoma, other female aged 31 years has recurrent cerebellopontin angle schwannoma, and other 48 years' female has inferior peduncular cystic lesion. This near to finding of *Cheng, et al., (1993)* who found that tumors occupying the posterior cranial fossa space, usually neuromas or meningiomas, are found in 2% of patients who present with typical TN. The localization of the tumor dictates the nature of facial symptoms. Tumors affecting the peripheral branches or the Gasserian ganglion usually give rise to sensory change leads to increased excitability and constant pain, in other words, trigeminal pain. Slowly growing tumors which distend the trigeminal root rather than invade it, are usually found in TN. In Cheng's series, the average delay in diagnosis of the tumor was 6.3 yr. Half of the patients developed sensory or motor deficits later *Nurmikko and Eldridge (2001)*. This can be explained by that trigeminal neuralgia is usually caused by demyelination of trigeminal sensory fibers within either the nerve root or, less commonly, the brainstem results from compression by a vascular compression or masses occupying the posterior cranial fossa space. Focal demyelination in the region of compression, with close apposition of demyelinated axons and an absence of intervening glial processes. Experimental studies indicate that

this anatomical arrangement favors the ectopic generation of spontaneous nerve impulses and their ephaptic conduction to adjacent fibers, and that spontaneous nerve activity is likely to be increased by the deformity associated with pulsatile vascular indentation. Decompression of the nerve root produces rapid relief of symptoms probably because the resulting separation of demyelinated axons and their release from focal distortion reduce the spontaneous generation of impulses and prevent their ephaptic spread. Remyelination may help to ensure that relief of symptoms is sustained after decompression of the nerve root and may also be responsible for the spontaneous remission of the neuralgia in some patients. In addition to causing symptomatic relief, decompression leads to rapid recovery of nerve conduction across the indented root (*Seth Love and Hugh Coakham, 2001*). On other hand 2 patients with ischemic stroke accidentally discovered to have a symptomatic cortical meningiomas not related for trigeminal neuralgic pain.

Polyneuropathy (PN) is seen in patient between ages of 23 and 32 {3 cases (4.2 %)} all of them have axonal changes in nerve conduction study, normal laboratory work, and MRI & MRA Brain. One of them is 25 years' male has left trigeminal neuralgia and long standing (PN) after infection during childhood period with wasting in tibialis anterior muscle. 2nd one is 32 years' male has eczema, left trigeminal neuralgia, right ulnar and femoral neuropathy. Other one of them was 23 years' female has right trigeminal neuralgia, short stature, paraparesis due to kyphoscoliosis in MRI dorsal region, normal MRI & MRA Brain but with 1st degree Arnold Chiari malformation. This go with *Nurmikko and Eldridge (2001)* report who reported that trigeminal neuropathy, whether painful or non-painful, is associated with structural lesion or systemic disease. Pain is usually constant and associated with allodynia and sensory loss.

One case (1.4 %) has TN and multiple sclerosis (MS) proved by MRI Brain and demyelinating changes in Evoked Potential modalities. This can be explained by finding of *Gass et al., (1997)* and *Heidi Godman and Ann Pietrangelo (2015)* who found brainstem demyelinating lesions affecting pontine trigeminal pathways in positions expected to involve trigeminal fibers, particularly the entry zone of sensory fibers in T2-weighted MRI brain in six patients with MS and TN. Focal demyelination and the resultant conduction aberrations (ephaptic transmission) are thought to represent the pathophysiological mechanism of the neuropathic pain of TN. MS plaques encompassing the root entry zone have also been described in pathological specimens of MS patients with TN (*Seth Love and Hugh Coakham, 2001*).

Injury to the trigeminal nerve (perhaps the result of sinus surgery, oral surgery, or facial

trauma) may also produce neuropathic facial pain. In this study, trigeminal pains after oral surgery is present in 2 cases (2.8 %) have normal MRI & MRA Brain one of them has mandibular hypoesthesia not recovered for 6 months. In this case supraperiosteal or proximal local anesthesia may result in injuries due to direct trauma to the nerve during infiltration of anesthetic solution from the needle, hematoma formation or neurotoxicity from local anesthetic solution to inferior alveolar nerve (IAN), lingual nerve (LN) or maxillary nerves. It has also been reported that anesthesia or paresthesia can occur in two-thirds of patients with permanent nerve injury involvement, whereas dysesthesia can occur one-third of such patients (*Smith, Lung, 2006, Maria Peñarrocha, et al., 2012 and Phoenix, 2017*).

Other patient has severe pain for years and was resistant to multiple neuropathic pain killers. (IAN) can be damaged during root canal treatment of the mandibular molar teeth, pressure in the IAN canal from endodontic point or neurotoxic effect of the medication used in the root canal (*Knowles et al., 2003 and Pogrel, 2007*). After root canal therapy, persistent pain was reported in 3-13% of cases *Polycarpou et al., (2005)*, whilst endodontic surgery ends with painful phantom tooth in 2% to 3% of cases (*Bennett, 2004*). Pathophysiology of trigeminal neuropathic pain after oral surgery is several types of sources as vascular compression, radiation, inflammation, trauma, infection, and exposure to neurotoxins to the peripheral nervous system can lead to pathologic damage. Demyelination and axotomy (deafferentation with severance of the axon) are the ways to incur these damages (*Devor, 2006, Spencer, and Gremillion, 2007, Neslihan Tinastepe, and Koray Oral 2013*).

Right trigeminal pain after physiotherapy for Bell's palsy is present in 2 cases (2.8 %) recovered after stoppage of electric stimulation for one week followed by decrease number of sessions to 2 sessions per week until recovery. However, *Benatar and Edlow (2004)* suggested that rarely, Bell's palsy can affect the trigeminal nerve. It's unclear whether facial numbness is due to an additional cranial neuropathy (trigeminal neuropathy) or altered sensation in the setting of a drooping face. Other cranial neuropathies are infrequent and should raise a high index of suspicion for stroke or other, more serious, causes of facial weakness.

Trigeminal pain after psychological stress is present in one case (1.4 %) had normal MRI & MRA Brain and has effective treatment in the form of Tricyclic antidepressants and Acetylsalicylic acid 81 mg. This go with finding of *Theoharides and Cochrane, 2004* who found that mast cells are involved in a variety of neuroinflammatory diseases, especially those worsened by stress. Mast cells appear to be activated through their Fc receptors by immunoglobulins other than Ig E, anaphylatoxins, neuropeptides and cytokines to secrete mediators

selectively without overt degranulation. These facts can help to understand a variety of sterile inflammatory conditions, such as migraines, multiple sclerosis (MS), inflammatory arthritis, atopic dermatitis, coronary inflammation, interstitial cystitis and irritable bowel syndrome, in which mast cells are activated without allergic degranulation.

Regarding laboratory finding in this work, elevated ESR level was found in 3 patients (4.2 %) 2 of them have ischemic strokes. Elevated ESR level, positive anti cardiolipin, and ANA were found in one female patient has history of arthritis, 2 abortions, multiple lacunar infarcts in MRI Brain with normal another lab. Work, MRA Brain, ECG, and ECHO, axonal changes in nerve conduction study, Visual Evoked Potential, Brain Stem Auditory Evoked Potential, Somatosensory Evoked Potential, and Somatosensory Trigeminal Evoked Potential. The pain paroxysms were suppressed with Pregabalin and anti-ischemic measure in this patient.

No test can determine with certainty the presence of trigeminal neuralgia. Tests can, however, help rule out other causes of facial disorders. Trigeminal neuralgia usually is diagnosed based on the patient's description of the symptoms, general, neurological examination, routine imaging study may be considered to identify a cause. In this study, normal MRI & MRA Brain is common in younger people (age ranged between 18 – 56 ± 33.9 years) 28 cases (38.4 %) 3 of them have polyneuropathy. Also, normal MRI with attenuated one of the vertebral arteries in MRA Brain is present in 9 cases (12.6 %) aged 38.3 ± 14.2 years. Also, this study found that 32 cases (43.8 %) have stroke etiology; 9 (12.6 %) have single stroke aged 47.56 ± 5, 24 (32.9 %) case have multiple infarcts aged 54.14 ± 18, and 5 cases of them (7 %) under age of 40. 3 of patients with stroke have attenuated one of the vertebral arteries in MRA Brain. 3 cases (4.2 %) have space occupying lesions (SOL) aged 39.67 ± 8.5. So routine neuroimaging (MRI ± MRA) identify a structural and serious underlying etiology; multiple sclerosis, stroke, tumors excluding compression of the trigeminal nerve by neurovascular lesion, brain aneurysm, arteriovenous malformation. This compression causes the wearing away or damage to the protective coating around the nerve (the myelin sheath). The introduction of new magnetic resonance techniques, such as voxel-based morphometry, diffusion tensor imaging, three-dimensional time-of-flight magnetic resonance angiography, and fluid attenuated inversion recovery sequences, has provided new insight about the TN pathogenesis. Some of these new sequences have also been used to better preoperatively evidence the neurovascular conflict *Montano, et al. (2015)*.

Conclusion:

Detailed history, clinical examination, and neuroimaging as MRI ± MRA brain are essential to

know etiology, diagnosis with subsequent effective treatment for patient with trigeminal neuralgia. Attenuated one or both vertebral arteries in MRA Brain, stroke, migraine, space occupying lesions, polyneuropathy, multiple sclerosis, oral surgery or Bell's palsy and it's physiotherapy are etiological factors for trigeminal neuralgia. Treatment of etiological factors, symptomatic control of pain and improvement of trigeminal nerve vasculature are essential for treatment of trigeminal neuralgia. Double-blinded trials are needed to assess local botulinum toxin injection for neuropathic pain.

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