

Novel and Conventional Causes of Trigeminal neuralgia and its impact on managementMahmoud Abdel-Moety Monzer¹ and Abdel-Salam El Ashry²¹Department of Neurology, Faculty of Medicine (For Boys), Al Azhar University, Cairo, Egypt²Department of Radiology, Faculty of Medicine (For Boys), Al Azhar University, Cairo, Egyptmahmoudabdelmoety@yahoo.com

Abstract: Background: Trigeminal neuralgia (TN) is usually a long-term condition may be idiopathic or symptomatic. Cerebrovascular stroke is the most common acute neurological illness responsible for a large proportion of the burden of neurologic disorders. **The aim of this study:** The aim is identification if there are new vascular etiology for trigeminal neuralgia and its impact on treatment of trigeminal neuralgia. **Subject and methods:** All patients were submitted to detailed history, clinical examination, scale for change in pain degree and neuroimaging as CT and / or, MRI ± MRA brain. Laboratory investigations, carotid and vertebrobasilar 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 62 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 (54.8 %) more affected than left side (37 %). Occasionally it affects both sides of the face in 8 % 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 87 % of cases, lower part of the face in 8 % of cases and upper part of the face in 4.8 % of cases. 95.2 % of patients have typical or “classic” form of trigeminal neuralgia TN1. TN2 is present in 8 % 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 6.4 % of cases, pyramidal signs are present in 14.5 % of cases and long sensory tract affection is present in 7.93 % of cases. Normal MRI & MRA Brain is present in 33.87 %. Normal MRI with attenuated one or both vertebral arteries in MRA Brain is present in 14.5 % of cases. Also, this study found that stroke etiology present in 51.5 % of cases and rare in people under the age of 40 (8 %) of cases but migraine is not rare (14.5 %) of cases. Hypertension, diabetes mellitus (DM), and dyslipidemia were risk factors for strokes. There was marked improvement of pain in nearly all patients indicated by presence of difference between pain intensity in the first visit and subsequent visits in patients with normal MRI and MRA Brain, patients with normal MRI and attenuated one or both vertebral arteries in MRA Brain and stroke groups for each. Also, there was a significant difference between these groups as regard recovery index being better in non-stroke group. **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 and ectatic vessels are vascular causes for symptomatic trigeminal neuralgia. Treatment of etiological factors, symptomatic control of pain and improvement of trigeminal nerve vasculature by antiplatelet as acetylsalicylic acid are essential for treatment of trigeminal neuralgia and prevention of development of strokes.

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Keywords: trigeminal neuralgia, Facial pain, causes, antiplatelet, stroke, migraine.

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*).

Stroke is one of the most common neurologic disorders, resulting in functional disorders and a high mortality rate in most developed and developing countries (*Larry et al., 2006*).

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 (*Pietrangelo, 2016*).

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. AICA irrigate mandibular part. Also, superior cerebellar, basilar and trigeminocerebellar share in their irrigation (*Cetković et al., 2011*).

Aim of the Work:

There are many patients their diagnosis well established as trigeminal neuralgia and had normal MRI scan and already received high dose of one (even starting complications of this medications) or many medications of neurogenic pain killer but pain didn't go away completely. Those patients didn't get any attack after Aspirin intake with gradual withdrawal of these medications. The aim of this work is to identify vascular etiology in trigeminal neuralgia and it is impact on treatment of trigeminal neuralgia.

Inclusion Criteria:

Patients with idiopathic trigeminal neuralgia and patients has or associated with vascular cause.

Exclusion Criteria:

Patients with symptomatic trigeminal neuralgia due to other causes other than vascular etiology (space occupying lesions, polyneuropathy, multiple sclerosis, oral surgery, other causes) or incorrect diagnosis {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} were excluded from the study.

2. Patients and Methods:

This retrospective study was carried out on 62 patients with trigeminal neuralgia. This study was carried out at the neurology department of Hay El-Gama hospital for 24 months.

All patients were submitted to:

1-Detailed medical and neurological history.

2-General medical examination.

3-Neurovascular examination.

4-Scale for change in pain degree in those patient with trigeminal neuralgia:

This involves a measurement of pain intensity in 3 categories (e.g. none, some and severe) (*Chen and Lee 2010*). Percentage decrease in pain degree in subsequent visits (recovery index is percent recovery score by calculating the percentage improvement of pain degree).

5-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 doppler for carotid & vertebrbasilar arteries:

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

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

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

8-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 for all patients with stroke. 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.

9-Neurophysiological assessment:

1-Nerve conduction study (NCS) was done for exclusion of patients with polyneuropathy other than with vascular etiology.

2-Visual Evoked Potential (VEP), Brain Stem Auditory Evoked Potential BAEP, Somatosensory Evoked Potential (SSEP), and Somatosensory Trigeminal Evoked Potential were done for one case has vasculitis and for exclusion of patients with multiple sclerosis.

10-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. Result:

This study was carried out on 62 patients with trigeminal neuralgia of different nationality. Trigeminal neuralgia affects females {32 cases (51.5 %)} more than males {30 cases (48.5 %)}. In the vast majority of cases {57 cases (91.9 %)} pain is limited to one side of the face, however right side more affected than left side {34, and 23 cases (54.8 and 37

%)}. Occasionally it affects both sides of the face in 5 cases (8 %) 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 54 cases (87 %), lower part of the face in 5 cases (8 %) and upper part of the face in 3 cases (4.8 %). Vast majority of cases of this study (58 patients {93.55 %}) 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 4 cases (6.45 %); 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 has attenuated one of vertebral arteries in MRA Brain.

There was marked improvement of pain in nearly all patients indicated by presence of difference between pain intensity (severe and some in pain score) in the first visit to (no pain in pain score) in subsequent visits in patients with normal MRI and MRA Brain, patients with normal MRI and attenuated one or both vertebral arteries in MRA Brain and stroke groups. Also, recovery index is improving especially in non-stroke group (many patients completely recovered without need for any pain killer medications in subsequent visits).

Regarding etiological factors for symptomatic trigeminal neuralgia in this study; trigeminal hypoesthesia is present in 10 cases (16 %) all of them has vascular etiology; 8 cases have ischemic stroke and 2 cases have attenuated one of vertebral arteries in MRA Brain (Figure 1). All three divisions of one side of the face are involved in 6 cases (9.6 %), 5 cases of them (8 %) have hemihypoesthesia. Lower part of the face is involved in 3 cases (4.58 %) followed by upper part of the face one cases (1.6 %).

Hearing affection is present in 4 cases (6.45 %) have ischemic stroke.

Facial spasm is present in one case (1.6 %) has ischemic stroke.

Pyramidal signs are present in 9 cases (14.5 %) all of them have ischemic stroke.

7 patients (11.3 %) were hypertensive also 7 (11.3 %) have diabetes mellitus. All of them have single, or multiple ischemic stroke and 2 of them have attenuated vertebral vessels. Migraine was found in 9 cases (14.5 %); 5 of them have ischemic strokes, and 5 have attenuated vertebral vessels.

In this study 32 cases (51.5 %) have stroke. Stroke is not rare in people under the age of 40 {5 cases (8 %)}. Deep parietal is the common site of infarction {19 cases (30.64 %)} then capsular {5 cases (8 %)}, followed by thalamic (figure 2), pontin, parietal {two cases (3.2 %) for each} and lastly lateral medullary and complete MCA occlusion {one case (1.6 %) for each} in patients of this study.

Trigeminal pain after psychological stress is present in one case (1.6 %) has normal MRI & MRA Brain.

Regarding laboratory finding in this work, elevated ESR level was found in 3 patients (4.8 %) 2 of them have ischemic strokes. Dyslipidemia was found in 2 patients (3.2 %) both of them 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.

From history taking, general, neurological examination, MRI & MRA Brain findings the patients are classified in this study into 3 groups:

Group (I) include 21 patients (33.87 %) their age ranged between 18 – 53 with a mean 32.14 ± 12 year (youngest people) in this study have normal MRI & MRA Brain.

Group (II) includes 9 cases (14.5 %) aged 38.3 ± 14.2 years with normal MRI and attenuated one or both vertebral arteries in MRA Brain.

Group (III) includes 32 cases (51.5 %) have stroke etiology; 23 (32.9 %) case have multiple infarcts aged (54 ± 18); 9 (14.5 %) have single stroke aged (47.56 ± 5) and 5 cases of them (8 %) under age of 40.3 of patients with stroke have attenuated one of the vertebral arteries in MRA Brain.

Visual Evoked Potential (VEP), Brain Stem Auditory Evoked Potential BAEP, Somatosensory Evoked Potential (SSEP), and Somatosensory Trigeminal Evoked Potential were done for one case has axonal changes going with vasculitis.

Significant carotid or vertebral artery stenosis was not found in any patient in this study.

Pharmacological Treatment: -

1-In this study anti-ischemic such as Acetylsalicylic acid 81 mg was given for all patients even with normal MRI & MRA Brain.

2-Systemic medications for neuropathic pain:

A-Anticonvulsant such as Carbamazepine, Oxcarbazepine, Gabapentin, Pregabalin, Phenytoin, Lamotrigine, Sodium valproate or Topiramate (by same sequence) are used and may be used in combination or with other drugs to achieve pain relief.

B-Antidepressant as Tricyclic antidepressants or Serotonin norepinephrine re-uptake inhibitor (SNRI) may also be effective and may be used in combination with other drugs to achieve pain relief in patient resistant to anticonvulsants especially in patients with depression.

3-Vit B1, 6, 12.

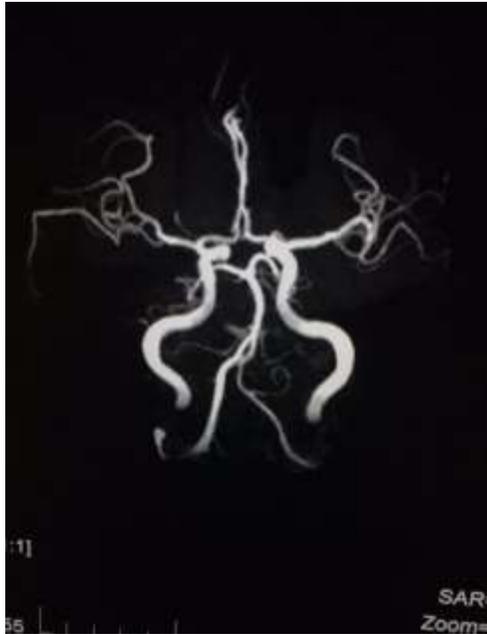


Figure 1

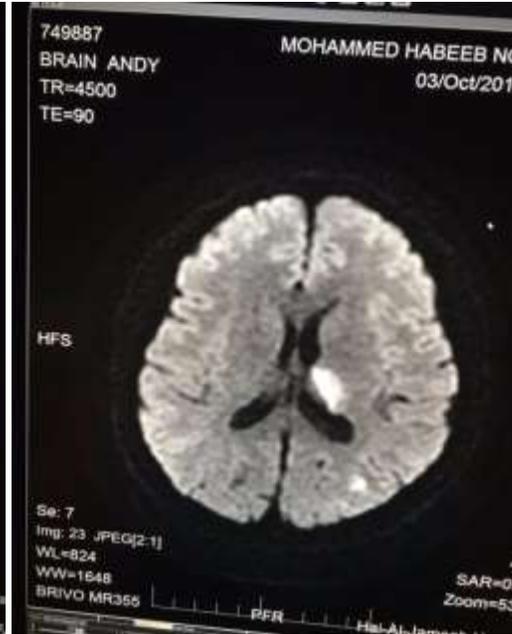


Figure 2

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

	Normal MRI & MRA Brain Group	Normal MRI Brain and Attenuated VA group	Stroke Group			P value	Statistical significance	
			Single stroke	Multiple strokes	Stroke with attenuated VA			
Number of patients	21 (33.87 %)	9 (14.5 %)	9 (14.5 %)	20 (32.2)	3 (4.8 %)			
Age	32.14 ± 12	38.33 ± 14.3	47.56 ± 5	54.14 ± 18	45.33 ± 4.6	<0.001	Highly significant	
Sex	Female 32 (51.6%)	14 (68 %)	5 (55.6 %)	2 (22.2 %)	11 (55 %)	0	> 0.05	Not significant
	Male 30 (48.38%)	7 (32 %)	4 (44.4 %)	7 (77.8 %)	9 (45 %)	3 (100 %)		
Side	Left 23 (37 %)	10 (52 %)	3 (33.3 %)	5 (25 %)	0		> 0.05	Not significant
	Right 34 (54.8 %)	10 (44 %)	4 (44.4 %)	6 (66.7 %)	13 (65 %)	3 (100 %)		
	Bilateral 5 (8 %)	1 (4.7 %)	2 (22 %)	0	2 (10 %)	0		
Division	All 54 (87 %)	20 (88.0%)	7 (77 %)	6 (66.7 %)	18 (90 %)	3 (100 %)		
	Lower 5 (8 %)	0	1 (11 %)	3 (33.3 %)	1 (5 %)	0	> 0.05	Not significant
	Upper 3 (4.8 %)	1 (4.7 %)	1 (11 %)	0	1 (5 %)	0		
Hypertension 7 (11 %)	0	0	4 (44 %)	1 (4.8%)	2 (66.7%)	<0.05	Significant	
Diabetes mellitus 7 (11 %)	0	0	4 (44 %)	1 (4.8%)	2 (66.7%)	<0.05	Significant	

Magnetic Resonance Imaging & Angiography Brain (MRI & MRA Brain).
Vertebral artery (VA).

4. Discussion:

Trigeminal neuralgia (TN) is the most common cause of neuralgic pain in the face, with an incidence of 3-5 cases per 100 000 people (Green 2007).

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 (Zakrzewska and 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).

Compression of the trigeminal nerve by ectatic vessels occupying the posterior cranial fossa space, a known cause of idiopathic trigeminal neuralgia which was not found in this study. 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 (*Love and Coakham 2001*).

Ischemic stroke is classified according to the causal conclusion into 5 main categories:

1. Macroangiopathy (Large artery atherosclerosis): Macroangiopathy is defined as the presence of an occlusion or stenosis with $\geq 50\%$ diameter reduction of a brain supplying artery corresponding to clinical symptom and with location and morphology typical of atherosclerosis on Doppler ultrasound or angiography.

2. Cardio embolism: is defined as the presence of a high or medium risk source of cardiac embolism, potential large artery atherosclerotic sources of thrombosis or embolism had to be absent.

3. Microangiopathy: Defined as the presence of one of the traditional lacunar syndromes. It is resulted from the occlusion of single perforating arteries with absence of acute cerebral cortical dysfunction.

4. Other determined etiologies: like vasculitis, hematologic disorders coagulopathies or other not further specified disease these diagnoses had to be refined by specific diagnostic studies.

5. Undetermined etiologies (despite extensive studies) (*Goldstein et al., 2001* and *Cupini et al., 2002*).

Acetylsalicylic acid is a nonsteroidal anti-inflammatory drug with antipyretic, analgesic, and antiplatelet activities, which are dose-dependent. Low doses have antithrombotic effects (irreversibly acetylate serine 530 of cyclooxygenase (COX)-1 so inhibits platelet generation of thromboxane A₂. Reduction of inflammatory cytokines can help relieve diabetic neuropathy; salicylate therapy could help reduce some of pro-inflammatory cytokines like COX-2, nitric oxide synthase, lipoxigenase, TNF alpha and a lot of pain-causing interleukins (IL-1, IL-2, IL-6, IL-8) as well as circulating glucose, triglycerides, C reactive protein and free fatty acids (*Abdulghafar 2015* and *Abramson 2016*).

Dipyridamole (inhibits the uptake of adenosine by platelets) and Clopidogrel inhibiting adenosine diphosphate (ADP) mediated platelet aggregation may be marginally more effective than aspirin in certain high-risk groups. However, there is evidence that adding a second antithrombotic agent, either an antiplatelet or an anticoagulant, to low-dose aspirin results in much greater risk reduction than replacing aspirin with another drug. Clopidogrel and extended-release dipyridamole produce additive beneficial effects when combined with low-dose aspirin in patients with ischemic cerebrovascular disease (*Patrono et al., 2004*).

GPIIb/IIIa receptors blockage could be a particularly desirable therapeutic strategy because,

first, the monoclonal antibodies to GPIIb/IIIa are more potent inhibitors of platelet function than aspirin; secondly, GPIIb/IIIa is platelet specific; thirdly, inhibition of GPIIb/IIIa still leaves platelet adhesion largely intact, contributing to haemostasis without causing thrombotic damage; and fourthly, the haemorrhagic diathesis produced by the inherited deficiency of GPIIb/IIIa receptors in Glanzmann thrombasthenia only rarely produces spontaneous brain haemorrhage, the most feared complication of anticoagulant and antiplatelet therapy. High-efficacy blockade of platelet GPIIb/IIIa with intravenous agents (abciximab, eptifibatide, tirofiban) and oral GPIIb/IIIa antagonists in the hope of extending the benefit to the long-term management of patients with acute coronary syndromes (*Coller, 1995, Patrono et al., 2004* and *Born and Patrono 2006*).

In this study, trigeminal neuralgia affects females more than males 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 14.5 % of cases aged 38.3 ± 14.2 years. Also, this study found that 8 % 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 57 cases (91.9%). Pain involve three divisions of the face in 54 cases (87 %), lower part of the face in 5 cases (8 %) followed by upper part of the face 3 cases (4.8 %). The right side is more frequently involved more than left side {34 & 23 (54.8 & 37 %) by same sequence} this go with finding of *Maarbjerg et al (2014)*. Occasionally it affects both sides of the face 5 cases (8 %) 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). Those characteristics include the presence of trigeminal sensory deficits and/or bilateral involvement. In this study, trigeminal hypoesthesia is present in 10 cases (16 %) 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 (9.7 %), 5 cases of them (8 %) have hemihypoesthesia. Lower part of the face is involved in 3 cases (4.2 %) followed by upper part of the face one cases (1.6 %).

Vast majority of cases of this study (58 patients {93.55 %}) 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 4 cases (6.54 %); 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 (1.6 %) has attenuated one of vertebral arteries in MRA Brain.

Hearing affection is present in 4 cases (6.4 %) have ischemic stroke.

Facial spasm is present in one case (1.6 %) has ischemic stroke.

Pyramidal signs are present in 9 cases (14.5 %) all of them have ischemic stroke.

7 patients (11.3 %) were hypertensive also 7 (11.3 %) 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 (51.5 %) have stroke. Stroke is not rare in people under the age of 40 {5 cases (8 %)}. Deep parietal is the common site of infarction {19 cases (30.64 %)} then capsular {5 cases (7.9 %)}, followed by thalamic, pontin, partial {two cases (3.2 %) for each} and lastly lateral medullary and complete MCA occlusion {one case (1.6 %) for each} in one patient for each in this study.

Symptomatic trigeminal neuralgia due to stroke in brainstem infarction is said to be rare. Facial pain related to pontin 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 *Ordás et al., 2011*). The generator of pain in other cases is located 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 (*Love and Coakham 2001*).

Migraine is present in (14.5 %) of cases in this study. It was known as unidentified risk factor for trigeminal neuralgia; *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 (14.5 %); 5 of them have ischemic strokes, 5 have attenuated vertebral vessels. This go with the same line with *Robert and Krusz, (2007)* and *Lin 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 *Pichiechio 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.

Headache often accompanies intracranial vertebral artery dissection (IVAD), and infrequently, it is the only symptom. Furthermore, IVAD presenting with isolated facial pain is rarer. Ischemia of the spinothalamic tract caused by IVAD is considered as the cause of facial pain. *Choi et al., 2016* and *Hanna and Choi et al., 2016* present a case of intracranial vertebral artery dissection with trigeminal neuralgia-like facial pain which was successfully treated with antiplatelet agents and Carbamazepine.

Trigeminal pain after psychological stress is present in one case (1.6 %) had effective treatment in the form of Tricyclic antidepressants and Acetylsalicylic acid 81 mg and has normal MRI &

MRA Brain. This goes 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 multiple sclerosis (MS), migraines, inflammatory arthritis, atopic dermatitis, coronary inflammation, interstitial cystitis and irritable bowel syndrome, in which mast cells are activated without allergic degranulation. However, depression is often seen in patients with trigeminal neuralgia; thus, this underlying depression should be adequately treated.

Regarding laboratory finding in this work, elevated ESR level was found in 3 patients (4.8 %) 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.

Normal MRI & MRA Brain is common in younger people (age ranged between 18 – 53 ± 32.14 years) 21 cases (33.78 %). Also, normal MRI with attenuated one of the vertebral arteries in MRA Brain is present in 9 cases (14.5 %) aged 38.3 ± 14.2 years. Also, this study found that 32 cases (51.5 %) have stroke etiology; 9 (14.5 %) have single stroke aged 47.56 ± 5, 23 (32.9 %) case have multiple infarcts aged 54.14 ± 18, and 5 cases of them (8 %) under age of 40.3 of patients with stroke have attenuated one of the vertebral arteries in MRA Brain. If trigeminal neuralgia occurs in younger people, this rise concern for potential structural cause this agree with report of *Flemming (2013)*. So routine neuroimaging (MRI ± MRA) may be considered to identify a cause especially if there is 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*). Otherwise, no test can determine with certainty the presence of trigeminal neuralgia.

Treatment of Trigeminal Neuralgia: -

Proper treatment and treatment of etiological factors are essential for treatment of trigeminal neuralgia. Discussing the treatment options with the patient will help to decide the most appropriate option.

1-Non-Pharmacological Treatment: -

Assessment and teach importance of oral hygiene, nutritional status, behavioral attitude, assess response to any drug therapy, careful pain assessment, keeping room at moderate temperature free of drafts, teaching about medications, appropriate teaching for surgical procedures. Complementary techniques like alternative medical therapies such as nutritional therapy, acupuncture (a Chinese tradition that uses very thin needles to balance the flow of energy in your body), aromatherapy (the use of plant oils such as peppermint, lavender, etc., to help healing), self-hypnosis, yoga and meditation may also help to alleviate symptoms. Advise patient to talk to his doctor before starting any alternative treatments, as these may interact with other medications (*Kiefer 2016*).

2-Pharmacological Treatment: -

There are many treatment options and combinations for trigeminal neuropathic pain, but the most important criteria are efficacy, safety, and favorable tolerability profiles (i.e., side effects, drug/drug interactions). In this study, there was marked improvement of pain intensity in nearly all patients with TN in comparison between first visit and subsequent visits also in all patient's groups. Improvement in idiopathic group is better (many patients recovered completely from pain without need for any medications for symptomatic control of pain in subsequent visits) with this regimen:

1- Anti ischemic measures: In this study, at least Acetylsalicylic acid 81 mg was given. It is given for all cases (even with normal MRI & MRA Brain). Also, it can be given or as polypharmacy in patient having attenuated vertebrobasilar system the main irrigating system for trigeminal nerve. However, most cases can be controlled with treatment in association with treatment of underlying condition, and pharmacological treatment of neuropathic pain of TN.

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, *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 *Haerter et al (2012)* on a murine model of familial hemiplegic migraine (FHM) revealed that FHM may increase stroke vulnerability by facilitating ischemic depolarizations.

2-Systemic medications for neuropathic pain:

❖ **Anticonvulsant** used to block nerve firing or at least calm down the nerve activity to reduce the pain and do not increase the risk such as Carbamazepine is stronger than oxcarbazepine in treatment of TN. However, the latter is safer. Gabapentin, Pregabalin, Phenytoin, Lamotrigine, Sodium valproate or Topiramate are other alternative effective option and may be used in combination or with other drugs to achieve pain relief in patient resistant to carbamazepine.

❖ **Antidepressant** as Tricyclic antidepressants or Serotonin norepinephrine re-uptake inhibitor (SNRI) may also be effective and may be used in combination with other drugs to achieve pain relief in patient resistant to anticonvulsants especially in patients with depression. Gabapentin might be also effective in symptomatic TN due to a brainstem infarction. In fact, gabapentin, pregabalin or amitriptyline are currently recommended for first line treatment in central neuropathic pain (*Attal et al. 2010*).

❖ **Muscle relaxant** as Baclofen, it's effectiveness may increase when it is used with either carbamazepine or phenytoin.

The medication to be effective needs to be taken several times a day, with the dose gradually increased over the course of a few days or weeks so that high enough levels of the medication can build up in your blood stream.

Unless your pain starts to diminish or disappears altogether, the medication is usually continued for as long as is necessary, sometimes for many years. If you are entering a period of remission and your pain goes away, stopping the medication should always be done slowly over days or weeks.

3-Vit B1, 6, 12.

4-Local botulinum toxin type A for neuropathic pain:

Hu et al (2013) and Cruccu and Truini, (2013) found a response in approximately 70 %–100 % of

patients with mean pain intensity and frequency reduced by approximately 60 %–80 % with no major adverse events after injection of botulinum toxin type A (BTX-A) in TN. It is preferred before surgery or to patients unwilling to undergo surgery. However, optimal dose of BTX-A treatment, the duration of therapeutic efficacy, the side effects, and the time and indications for repeat injection, further randomized, controlled, double-blinded trials are needed.

5-Surgical techniques:

If condition is progressive; attacks often worsen over time, with fewer and shorter pain-free periods, the pain-free intervals disappear and medication to control the pain becomes less effective or if they produce undesirable side effects, neurosurgical procedures are available as decompression by opening skull and move away any blood vessels compressing the trigeminal nerve or reduce nerve sensitivity by minor surgical procedures by damaging the nerve to stop it sending pain signals by Rhizotomy (percutaneous techniques, Gasserian ganglion) or gamma knife but these are generally only effective for a few years to relieve pain. Decompression operation offers the best results in terms of long-term pain relief, but it is a major operation and carries a risk of potentially serious complications, such as hearing loss, facial numbness or very rarely stroke or even death (*Kiefer 2016* and *Singh, 2016*).

Patients opt to have surgery which may or may not be effective. Pain free periods after surgery vary. Sometimes surgery exacerbates the pain. Which surgical technique gives the longest pain-free period with the fewest complications and good quality of life? There is weak evidence to support that early surgical therapy may be considered for patients with TN refractory medical therapy.

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 and ectatic vessels are vascular causes for symptomatic trigeminal neuralgia. Treatment of etiological factors, symptomatic control of pain and improvement of trigeminal nerve vasculature by acetylsalicylic acid are essential for treatment of trigeminal neuralgia and prevention of development of strokes. Double-blinded trials are needed to assess patients with and without acetylsalicylic acid and its effect for neuropathic pain.

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