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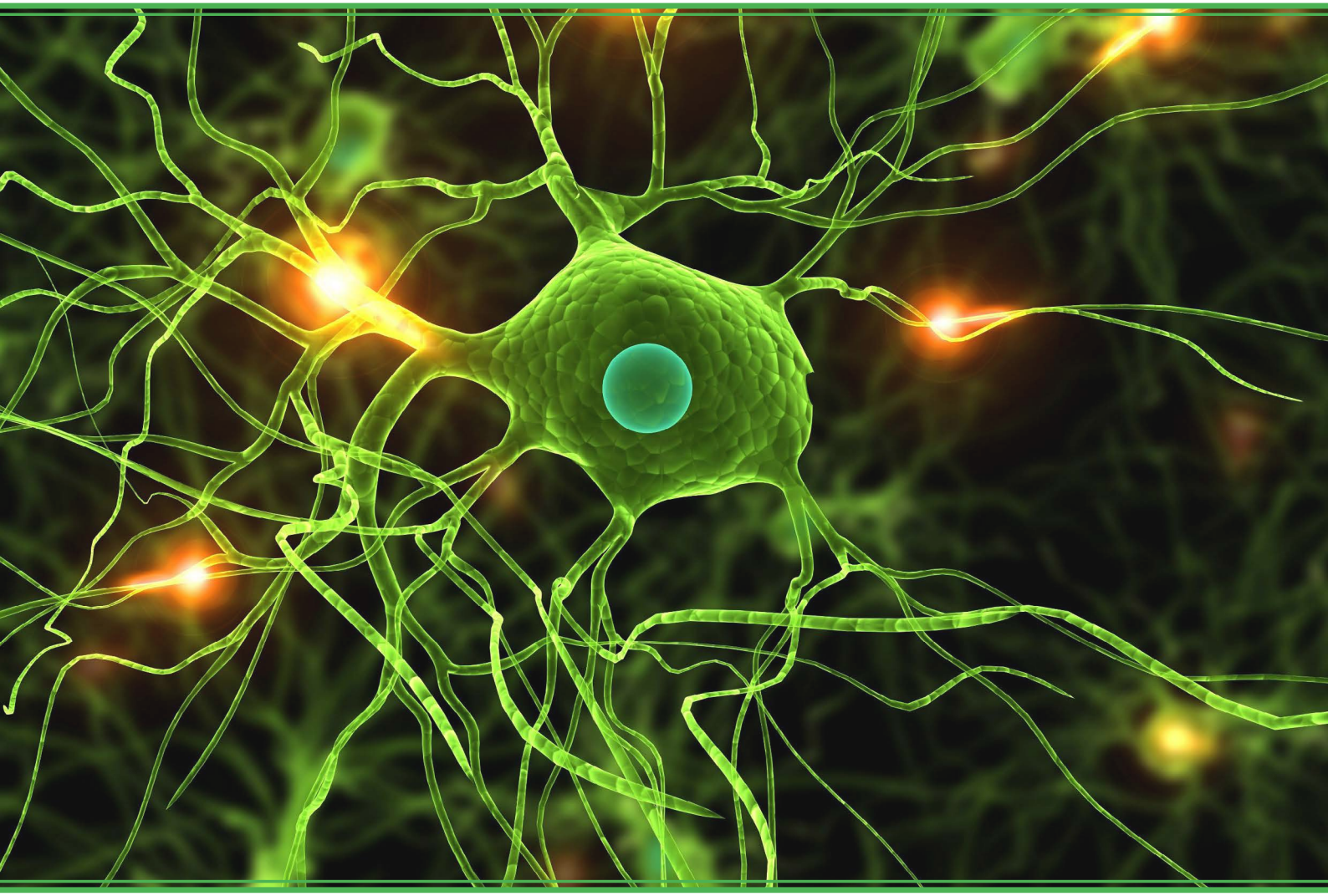
ISSN 2377-1607

NEURO

Open Journal

| October 2015 | Volume 2 | Issue 3 |



NEURO

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ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-e004

Editorial

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Volume 2 : Issue 3
Article Ref. #: 1000NOJ2e004

Article History:
Received: October 26th, 2015
Accepted: November 18th, 2015
Published: November 18th, 2015

Citation:
Samsam M. Targeting calcitonin gene-related peptide and its receptor by monoclonal antibody, new developments in the prevention of migraine. *Neuro Open J*. 2015; 2(3): e6-e10.

Targeting Calcitonin Gene-Related Peptide and its Receptor by Monoclonal Antibody, New Developments in the Prevention of Migraine

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KEYWORDS: Migraine; Calcitonin Gene Related Peptide (CGRP).

Migraine is a chronic headache disorder with an unknown pathophysiology. Research in the past decade has shown that to be a brain disorder, a dismodulation of sensory processing affecting vascular tone and pain[1-3] but since the exact pathomechanism of migraine is not very well known, its treatment is also difficult. Current drugs recommended by the "European Federation of Neurological Societies (EFNS)" used in the treatment of migraine include the triptan family drugs that are serotonin (5-$HT_{1B/D}$) receptor agonists, and the Non-Steroid Anti-Inflammatory Drugs (NSAIDs).[4] Several other drugs such as anti-epileptic drugs, beta-blockers, and calcium channel blockers are also recommended in the treatment of migraine.[4]

Although glutamic acid is one of the main neurotransmitters in the sensory system, various neuropeptides have been implicated in pain but among them, Calcitonin Gene Related Peptide (CGRP) is the only one neuropeptide that was found elevated in the blood of migraine patients[5-7] and CGRP administration induces migraine-like attack in migraine patients.[8] Therefore, several studies in the last decade focused on drugs to block the CGRP receptor[9-11] or the effect of CGRP itself by antibodies against it[10-12] although, it is not clear if the site of action of these drugs is peripheral or central.[13]

Nevertheless, triptan family drugs are currently some of the best and most potent compounds in the treatment of migraine,[4,14] but not all patients respond to them and search for other drugs that lack vasoconstrictive activity has continued. The discovery of CGRP-receptor antagonist drugs,[15] the so called "gepant family drugs" such as telcegepant and olcegepant, and BI 44370 TA were the main events in migraine research in the last decade.[16-21] Unfortunately, these drugs were discontinued due to their side effects such as hepatotoxicity although they were able to treat migraine effectively. Nevertheless, some newer drugs in this category including MK-3207,[22,23] BMS-846372[24,25] and MK-1602[26] are still under investigation, see[10] for a brief review. Nevertheless, research in the treatment of migraine did not stop here and search for other drugs being able to block CGRP or its receptor continued.

CGRP receptor is a hetero-oligomeric complex that has a peculiar structure and consists of a component, called the "Calcitonin receptor-like receptor (CLR)" which is a transmembrane Gs protein-coupled receptor, and an accessory protein component known as the "Receptor Activity-Modifying Protein 1 (RAMP1)" for the transport of CLR to the plasma membrane, and another component known as "Receptor Component Protein (RCP)" that is important for signaling pathway by determining the G-protein to which the receptor should be coupled with.[10,27,28]

In recent years, monoclonal Antibodies (mAbs) against CGRP or its receptor have been developed and are the newest anti-migraine drugs in clinical trials.

Monoclonal Abs against CGRP remove the excess peripheral CGRP that is released from the perivascular nerve endings and mAb against CGRP receptor prevents the CGRP signalling cascade.[10-12,29-31] Please see[31] and corresponding references for a brief review of the structure of CGRP and its receptor and related signalling molecules.

At the moment, there are three anti-CGRP mAbs examined in clinical trials. These include the LY2951742 that has been developed by Eli Lilly and Company,[32] ALD-403 that has been developed by Alde Biopharmaceuticals[33] and TEV-48125 (LBR-101), developed by Teva Pharmaceuticals.[34] The other class of mAb is against CGRP receptor complex, the AMG 334 that has been developed by Amgen.[35]

Although these drugs are still in clinical trials, LY2951742 and ALD-403 have both shown to decrease the mean migraine days per month from baseline compared to placebo group.[36,37] The LY2951742 is a humanized mAb against CGRP with a half-life of 28 days and was given subcutaneously (150 mg once every 2 weeks for 12 weeks) to migraine patients. Migraine days decreased from 4-14 days per month. This decrease was 4.2 days in drug treated group compared to the placebo treated group who had 3.0 days decrease in headache days per month in the 3rd month;[36] that is 1.2 day difference in migraine headache although, there this decrease was evident from the first month.[36]

The ALD-403 is also a humanized mAb against CGRP with a half-life of 31 days and was given as a single i.v. dose (1000 mg per 3 month).[37] Migraine days decreased from 9-10 days of headache per month that 8-9 of them qualified as migraine days. This decrease was 5.6 days in drug treated group compared to the placebo treated group who had 4.6 days decrease in headache days per month in the 3rd month;[37] that is 1 day difference in migraine headache nevertheless, decrease in migraine days started from the first month.[37] TEV-48125 (LBR-101) is also a humanized mAb against CGRP that has a half-life of 45 days. It has been used at 0.2- 2000 mg given in a one hour i.v. infusion as a single dose once on day 1, or up to 300 mg twice on day 1 and 14. It is now in clinical trials phase 2 and has been reported to reduce the migraine days.[12,38] The phase 2b clinical trials will be based on a 1-month run-in phase which is followed by one subcutaneous injection per month for 3 months.[12]

The other drug in this category is the AMG 334, a mAb against CGRP receptor. It is under clinical investigation and analysis but reduction in migraine days per month has been reported.[39]

Please see[10-12,31] for brief review of the drugs against CGRP and its receptor and some of the biological activities of CGRP.[31]

Another interesting pathway is activation of Vanilloid receptor 1 (transient receptor potential action channel subfamily V member 1, TRPV1) and release of sensory neuropeptides such as CGRP.[40] Similarly, inflammatory conditions can activate the TRPV1 receptor resulting in CGRP release[41] therefore, blocking TRPV1 has been one of the goals of some scientists in the treatment of pain in the last couple of years.[42,43]

Inhibition of TRPV1 receptor or interfering with the CGRP effect improves health and increase longevity in mice.[44] Can mAbs against CGRP has other effects?

Nevertheless, in addition to targeting CGRP or its receptor with mAbs several other new drugs in clinical trials such as 5-HT_{1F} receptor antagonist, drugs targeting nitric oxide synthase, glutamate, or GABA-A as well as invasive and noninvasive neuromodulation are under investigation for the treatment of migraine, please see[45,46] for review.

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ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-116

Mini Review

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Volume 2 : Issue 3
Article Ref. #: 1000NOJ2116

Article History:
Received: September 14th, 2015
Accepted: September 30th, 2015
Published: October 1st, 2015

Citation:
Gonzalez MJ, Yock-Corrales A. Stroke Mimics in the Pediatric Population. *Neuro Open J*. 2015; 2(3): 74-78.

Stroke Mimics in the Pediatric Population

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ABSTRACT

Pediatric stroke is a very rare condition and it is a cause of significant morbidity and mortality. It is among the top ten causes of death in the pediatric population, and over half of stroke survivors experience long-term disabilities. One major challenge in the diagnosis of stroke is the fact that there are many conditions that may mimic stroke. In the pediatric population the incidence of stroke mimic is around 79-93% of all presentations of acute focal brain dysfunction. The most common diagnosis in children is complicated migraine, seizures disorders, Bell's palsy and conversion disorders. The aim of the evaluation of these conditions is to rule out the diagnosis of acute stroke and the computed tomography (CT) is the modality of choice as is more accessible in the Emergency Departments (ED).

KEYWORDS: Stroke mimics; Children; Stroke.

ABBREVIATIONS: CT: Computed Tomography, ED: Emergency Department, MRI: Magnetic Resonance Imaging.

INTRODUCTION

Pediatric stroke is an uncommon condition and it's a cause of significant morbidity and mortality. It is among the top ten causes of death in the pediatric population, and over half of stroke survivors experience long-term disabilities.[1] Children with stroke experience impairments that interfere with normal development and living.[2,3]

The incidence of pediatric stroke is rare with an estimation of 2 to 3 per 100, 000.[4] Due to the rarity of the condition, recognition and diagnosis of pediatric stroke is often delayed. Studies locally and overseas have consistently demonstrated a considerable time lag of more than 20 hours.[5-8]

Besides pediatric stroke being rare, another major challenge in the diagnosis is the fact that there are many conditions that may mimic stroke. Stroke mimics are defined as non-vascular conditions with a stroke-like presentation that are suggestive of acute focal brain dysfunction.[9] In the adult population the stroke mimics account for approximately 30% of patients that are assessed for focal brain dysfunction of apparently abrupt onset. Brain attacks is the named given for this condition in the adult literature.[10] According to some case series, in the pediatric population the incidence of stroke mimic is 79-93% of all presentations of patients with acute neurological symptoms.[11,12]

CLINICAL RELEVANCE

From the many patients that present with neurological symptoms in a pediatric ED, there are the ones who require neuroimaging in order to rule out a diagnosis of stroke. Within this pool of patients, there are a small number of actual stroke cases. Thus, there is a need to differentiate these stroke mimics, primarily important for the acute treatment and for the rapid management of the actual stroke cases.

ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-116

Currently, there is a lack of data in the literature describing pediatric stroke mimics and there are only few studies published.[11-13] In the study by Shellhaas, et al., they compared benign diagnoses (one third of mimics) with non-benign diagnoses within the "mimics" group, and found no difference except for the presence of seizures in benign disorders. The main presenting signs were seizure, focal weakness and headache. Diagnoses of the mimics were diverse and included complicated migraine, seizures disorders, psychogenic diagnoses and musculoskeletal abnormalities. Limitations noted by the author's were that not all stroke mimics were referred to the stroke team for evaluation. Additionally, the number of mimics included in the study (n=30) was small, and it wasn´t a representative sample.[11]

In the study by Mackay, et al., they review prospectively all patients that presented to a pediatric ED with brain attacks and found that the spectrum of diagnosis in children is different from adults; being the most common diagnosis in children complicated migraine, seizures disorders, Bell's palsy and conversion disorders. This data was more representative with 301 consecutive presentations of brain attacks in a pediatric ED where immediate decisions need to be made for imaging and acute management.[12]

Reported incidence of these stroke mimics in adults range from 4.8% to 31%.[9,10,14,15] A paper on adult stroke mimics lists intracranial mass lesions, seizures with post-ictal states, migraines, psychiatric disorders, hypoglycemia and encephalopathy as mimics of stroke in adults.[16]

Another study in adults by Vroomen, et al., looked at the incidence and scope of stroke mimics presenting to a stroke department. In those patients younger than 50 years old, a fifth had a stroke mimic. In this age group, the main mimics were conversion disorder and migraines. In those above 50 years old, mimics were much less common (3%). Besides conversion disorder and migraines, epilepsy was also a major stroke mimic in this age group.[15]

In the study by Hand, et al., they also attempted to determine the nature of stroke mimics, in order to allow differentiation between stroke and mimics at the bedside of the patient.[10] In this study, the proportion of stroke mimics was around 30%. One of the strengths of this study was that they found 8 items that independently predicted the diagnosis in "brain attack" patients. This included findings that mimics are more likely with a history of cognitive impairment, loss of consciousness, seizures at onset, no lateralizing symptoms, no focal neurology and signs in non-vascular systems. On the other hand, patients with definite focal symptoms, an exact time of onset and those who were well the week before were more likely to have a stroke.[10] Other strength was that it gives physicians tools to identify the reliable (and unreliable) components of a clinical assessment in the bedside when assessing patients with a possible stroke. One limitation was that the information was obtained only from the patient and didn´t include the data given by family members or emergency physicians.[10]

Children	Adults
1. Complicated Migraine	1. Epilepsy/Seizures
2. Epilepsy/Seizures	2. Systemic Infections
3. Bell´s Palsy	3 .Migraine
4. Psychiatric causes	4. Toxic-Metabolic
5. Syncope	5. Peripheral Nervous System/ Mononeuritis
6. Non-specified Headache	6. Psychiatric causes
7. Cerebelitis	7. Encephalopathy
8. Peripheral Nervous System/Mono-neuritis	8. CNS Tumors
9. Drug intoxication	9. Vestibular

Table 1: Comparison of Stroke Mimics in order of frequency in adults and children.

Modified from Mackay MT, et al. Stroke and nonstroke brain attacks in children. Neurology. 2014 Apr 22; 82(16): 1434-40.[12]

COMMON DIAGNOSIS OF STROKE MIMICS

Migraine

Headaches and migraines are common health problems in children, and have been reported to occur in 10.6% of children aged between 5 to 15 years, and even greater numbers in older children (28% in 15 to 19 year-olds).[17] Some rare migraine variants are found in childhood. These include ophthalmoplegic migraine and alternating hemiplegic migraine. Ophthalmoplegic migraine may involve the 3rd, 4th and/or 6th cranial nerves and generally presents with transient migraine-like headaches with associated nerve neuropathy, such as diplopia.[18] Alternating hemiplegic migraine (or alternating hemiplegia of childhood) is a rare syndrome of episodic hemiplegia lasting minutes to days, with accompanying dystonia, nystagmus, oculomotor abnormalities and cognitive impairment.[19] These syndromes and their associated neurologic deficits may present a diagnostic challenge, especially in the evaluation of a possible stroke.

Bell's Palsy

Bell's palsy is a common cause of facial paralysis and is a self-limiting disease that has a generally benign course. While its pathophysiology is unknown, inflammation and compression of the facial nerve in its passage through the facial canal remains the popular theory, but acute immune demyelination triggered by a viral infection may be the reason behind the disease. The sudden onset of Bell's palsy causes patients to seek medical attention urgently and it is the role of the emergency physician to exclude other neurological causes of facial paralysis, such as stroke.[20]

ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-116

Todd's Paresis

Todd's paresis (or Todd's paralysis) is a neurological event in which a period of paralysis, involving usually one side of the body, occurs after a seizure. These episodes may last from minutes to hours and the patient's speech and vision may also be affected. Its presentation is similar to that of stroke and thus careful investigation and differentiation is necessary.[21]

Conversion Disorder

Other mimics of stroke include psychological disorders such as conversion disorder, which is a condition that presents with altered physical functioning, but with an underlying psychological cause. Common presentations are weakness, involuntary movements and sensory disturbances. Children with conversion disorder may have a history of abuse, and some may have family members with conversion disorder. A study in children and adolescents with acute conversion symptoms concluded that reduced effective attention, executive function, and memory are associated in these patients.[22]

Evaluation and Management

In the evaluation of stroke mimics the main aim is to rule out the diagnosis of stroke and initiate immediate treatment according to the diagnosis suspected. It is well known that in the pediatric population the delays in seeking medical advice, lack of awareness of health workers and the non-abrupt onset of symptoms make the diagnosis of this disease very delayed.[5,6,23]

Risk factors for pediatric stroke are different from those in adulthood. At initial presentation, approximately half of the children who presented with stroke had no previous positive medical history, but once admitted and when investigations are done some will have unexpected pathologies such as primary cerebrovascular disease or may have modifiable risk factors such as hypertension associated with sickle cell disease.[24] In children, a more direct cause–effect relationship between risk factors and stroke events exists, in comparison with adults, in whom risk factors such as smoking, obesity, hypertension, and diabetes cause stroke indirectly *via* the acceleration of atherosclerosis.[25]

In children, the clinical presentation of stroke is variable and may be non-specific, contributing to decreased recognition by physicians.[5] Subtle signs and symptoms of in co-ordination, limb weakness and lethargy are easily attributable to conditions besides stroke, such as normal clumsiness and behavioral issues. Presentation of stroke is related to the age of the child and the location of the infarct.[1]

In terms of interpreting the signs and symptoms at presentation, it is essential to understand the normal developmental stages of a child. Subtle signs and symptoms in infants and younger children tend to be missed, and stroke is picked up only when more obvious gross neurological deficits developed. In the younger age group like neonates and infants, the more common symptoms on presentation are seizures and lethargy. For older children, focal deficits like hemiparesis are often the main complain on arrival.[7,26,27]

Stroke is diagnosed primarily by neuroimaging evidence of infarction in a cerebral artery territory, considered together with clinical history and examination findings. A systematic evaluation should aim to exclude mimics and to identify the stroke etiology.[1] To this end, evaluation should include taking a detailed personal and family medical history (e.g. coagulopathies, cardiac disorders) and questions about recent events like trauma and infections to assess possible risk factors for stroke. A thorough neurological examination should seek to identify all abnormalities, both gross and subtle. This is especially important in younger patients where subtler signs like limb weakness can be easily missed.

The imaging use to confirm or in this case rule out stroke include Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scans of intracranial structures and also blood vessels imaging (angiography). Widely available in most emergency department settings, CT is usually helpful for distinguishing the different possible diagnosis.[28] However, an early infarct may not show up on CT, thus MRI, whether conventional or diffusion-weighted, is the preferred imaging method in the evaluation of possible stroke.[27] If the patient is still in the ED the CT is the modality of choice as is more accessible.

Other studies that are helpful when suspected stroke mimics are electroencephalogram for seizure disorders and evoke potential test for neuropathies or conversion disorders. More evaluations needed should be individualized according to the possible diagnosis suspected by the physician.

The need for early consultation with a neurology specialist might be useful in helping the clinician (usually an emergency doctor) to determine who have a probable stroke. This early assessment will improve the times from onset of symptoms to diagnosis of stroke and will help in initiating treatments of some cute stroke like syndromes in the pediatric population.

CONCLUSION

There is currently not much literature about the incidence of stroke mimics in the pediatric population, their presenting signs and symptoms. Therefore, more studies are needed to help the physician not only to increase awareness about pediatric stroke but also to help differentiate between the mimics and the actual stroke cases.

Adult studies may not be directly applicable for pediatric stroke as there are differences in presentation between adult and childhood stroke mimics. Also, the incidence of adult stroke mimics differ from that in children, with a higher propor-

tion likely in the pediatric population associated to numerous diagnostic challenges in younger patients.

Limited awareness regarding pediatric stroke among physicians and in the community is a major issue in the diagnosis not only of stroke but also stroke mimics. There are no brain attack protocols in children, specifically a well-established diagnostic pathway from pre-hospital setting to the hospital setting. In the future, the initiative of an ED stroke-screening tool in all the acute settings, will aid in the prompt recognition of stroke patients and improvement in their management like using thrombolysis as acute management for this disease as standard practice.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

SOURCE OF FUNDING: None.

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ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-117

Review

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Volume 2 : Issue 3
Article Ref. #: 1000NOJ2117

Article History:
Received: September 10th, 2015
Accepted: October 6th, 2015
Published: October 7th, 2015

Citation:
Samsam M. Drugs against calcitonin gene-related peptide and its receptor used in the treatment of migraine: What are the new progresses? *Neuro Open J*. 2015; 2(3): 79-91.

Drugs Against Calcitonin Gene-Related Peptide and its Receptor Used in the Treatment of Migraine: What are the New Progresses?

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ABSTRACT

Migraine is a chronic headache disorder that its exact pathomechanism is not very well known but research in the last two decades indicates that it might be a brain disorder, a dismodulation of sensory processing of the brainstem responsible for regulation of vascular tone and the pain. Several neurotransmitters and neuromodulators including neuropeptides have been implicated in the pathomechanism of migraine, among them, Calcitonin gene-related peptide (CGRP) has been the focus of many studies in recent years. Increased CGRP level (perhaps due to release from peripheral and central sensory nerve endings) has been detected in the blood of migraine patients and many basic and clinical investigators in recent years have been trying to block the CGRP receptor by means of newly developed CGRP-receptor antagonist drugs or inhibit its activity by even newer compounds, the monoclonal Antibodies (mAbs) against CGRP or its receptor. These latter ones are still in clinical trials but have had promising results so far in alleviating the pain of migraine patients. This article will briefly review and discuss the role of CGRP and its receptor in migraine and some of the other biological activities of CGRP, the CGRP receptor antagonist drugs and the new progresses in mAbs against CGRP or its receptor.

KEYWORDS: Migraine; Calcitonin gene-related peptide.

ABBREVIATIONS: CGRP: Calcitonin gene-related peptide; mAbs: monclonal Antibodies; TG: Trigeminal Ganglion; NSAIDs: Non-steroid anti-inflammatory drugs; CLR: Calcitonin receptor-like receptor; RAMP1: Receptor activity-modifying protein 1; RCP: Receptor Component Protein; TNF: Tumor Necrosis Factor; IL-10: Interleukin-10; TLR4: Toll-like receptor 4; eNOS: endothelial Nitric Oxide Synthase; ASD: Autism Spectrum Disorders; RNA: Ribonucleic acid; BBB: Blood Brain Barrier.

INTRODUCTION

Migraine is believed to be a brain disorder, a deficiency of sensory modulation, and probably a system failure of normal sensory processing of the brainstem that regulates the vascular tone and the pain in migraine.[1,2] Although the aura phase of migraine is believed to be due to cortical spreading depression, a similar mechanism of neuronal excitation is believed to be the trigger for migraine while the headache phase of migraine seems to involve the trigeminovascular system consisting of mainly trigeminal nerve and meningeal vessels.

Observations of Dr. Goadsby and several investigators using imaging studies suggest that the trigger phase of migraine is initiated by neuronal hyperexcitability and activation of the brainstem, hypothalamus, and the brain, and that activation is often unaffected even after relief of the headache by antimigraine drugs.[3-5]

ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-117

A major part of the dura mater specially the supratentorial part of dura is innervated by the trigeminal nerve, mainly the ophthalmic branch. The Trigeminal Ganglionic (TG) neurons contain several neurotransmitters and neuromodulators among them glutamic acid and various neuropeptides including the calcitonin gene-related peptide.[6,7] Several neuropeptides coexist together in TG sensory neurons and may be released at the first central trigeminal synapses in the brainstem upon stimulation,[8] but clinically, significant CGRP increase has been seen in migraine patients.[9,10] CGRP administration in human provoked a migraine-like attack in migraine patients[11] and CGRP-antagonists alleviated the headache to a comparable level to other potent anti-migraine drugs such as sumatriptan.[12] Currently, some of the first choice antimigraine drugs include the triptan family drugs that are the serotonin receptor agonists (5-$HT_{1B/D}$), and the Non-steroid anti-inflammatory drugs (NSAIDs) according to the "European Federation of Neurological Societies (EFNS)".[13] Please see[14-16] for a comprehensive review of the triptan family drugs and their receptors, and see[5,17] for a brief review of several other drugs that are being used for the treatment of migraine including their actions, effects and side effects.

However, research in the treatment of migraine is one of the active fields of the neurological research and several studies in recent years focused on new and alternative treatment strategies including antagonizing CGRP receptors and/or blocking the CGRP activity by mAbs against CGRP and/or its receptor.

Calcitonin gene-related peptide consists of 37 amino acid detected by alternative processing of Ribonucleic acid (RNA) transcripts from the calcitonin gene which result in the production of distinct messenger RNA (mRNAs) that encodes the hormone calcitonin.[18]

There are two forms of CGRP in humans: the α-CGRP and the β-CGRP that are derived from different genes that differ in 3 amino acids but show similar functions.[19] The α-CGRP is expressed in sensory neurons including the trigeminal ganglion and is the relevant one in migraine pathophysiology while the β-CGRP is expressed in the enteric nervous system and in hypophysis and its role in migraine is not known.[20-22]

There is a wide anatomical distribution of CGRP in the body including the central and peripheral nervous system and is involved in many functions including nociception, glucose uptake, and stimulation of glycolysis in the skeletal muscles.[23] CGRP is a potent vasodilator in human and rat and may mediate hyperemia in some pathological conditions.[24]

The headache phase of migraine is believed to be caused by vasodilation of cranial vessels activating the trigeminal and other sensory nerves,[25-28] although migraine has been reported without the initial dilatation of the middle cerebral artery[29] and even during cerebral hypoperfusion.[29-32]

CGRP Receptor and its Localization in the Nervous System

CGRP receptor has an unusual structure and consists of a hetero-oligomeric complex with a transmembrane Gs protein-coupled receptor, the "Calcitonin receptor-like receptor (CLR)" and an accessory protein known as the "Receptor activity-modifying protein 1 (RAMP1)" which is necessary to transport CLR to the plasma membrane. Both the CLR and RAMP1 subunits have extracellular domains that interact with one another and together form a complex for the peptide-binding site.[33-36] The extracellular domain of RAMP1 is very important for the binding of CGRP-receptor antagonist molecules to the CGRP receptors[37] and function of RAMP1 is crucial for the activity of CGRP receptor in the trigeminal ganglion.[38] Another related structure of the CGRP receptor is the Receptor Component Protein (RCP) which is crucial for signaling pathway and determines the G-protein to which the receptor should be coupled with.[29,35]

The CLR acts as a receptor for either CGRP or adrenomedullin, depending on which members of RAMPs are expressed. RAMP1 is a CGRP receptor at the cell surface and acts as a mature glycoprotein as well. RAMP2-transported receptors are adrenomedullin receptors and are core-glycosylated molecules.[33,39]

Although originally two CGRP receptors (1 and 2) were recognized[40] the nomenclature changed later and the "CGRP(1)" receptor is now known as the "CGRP" receptor.[17,41]

Various signaling molecules and second messengers are involved following the CGRP receptor activation. These include the CGRP activation of ATP-sensitive K^+ channels[42] or large-conductance Ca^{+2}-activated K^+ channels[43] with a subsequent increase of intracellular cAMP[44] leading to vasodilation and headache. Nitric oxide activation of CGRP release in trigeminal ganglion neuronal cell culture however involves extracellular calcium and T-type calcium channels.[45]

CGRP receptor (both CLR/RAMP1 components) mRNA and protein are expressed in several regions of the CNS including the spinal cord and spinal trigeminal nucleus, area postrema, pineal gland, parts of hypothalamus, periaqueductal gray matter, pontine raphe nuclei and the gracile nucleus although the RAMP1 mRNA was also detected in several regions of the brainstem and that CGRP receptor was found in areas that were not supported by BBB.[46]

CGRP receptor is also expressed in the cerebellum.[47] Localization of the CGRP receptor in the tigeminovascular system seems to be on the central trigeminal nerve endings, dural blood vessels and mast cells, and trigeminal ganglion[48,49] as well as dorsal horn secondary neurons.[50] Please see[22,46,51] for a comprehensive review of the CGRP receptor sites. CNS glial cells such as astrocytes and microglial cell[52] and Schwann cells[49] also express CGRP receptors as well.

CGRP Receptor Antagonists in the Treatment of Migraine

One of the important properties of CGRP-antagonist drugs such as BIBN4096BS is that it prevents the CGRP-mediated vasodilation or activation of trigeminovascular afferents[53] without the vasoconstrictor activities which is an advantage in patients with coronary heart disease or in patients with second rebound attack, see[53,54] for review.

The discovery of CGRP-antagonist drugs the "gepant" family, in the last decade was a breakthrough in migraine treatment research due to their lack of vasoconstrictive activity compared to some "triptan" family drugs. One of the first drugs, the BIBN4096BS, also known as olcegepant, prevents the CGRP-mediated vasodilation or activation of trigeminovascular afferents,[12] and presumably inhibits the central CGRP receptors.

Olcegepant is a potent anti-migraine drug that has been examined on human arteries.[55-59] The BIBN4096BS was shown to block the responses evoked by stimulants such as α-CGRP and capsaicin, or transcranial electrical stimulation of perivascular trigeminal nerve[60] which reduces the increased dural blood flow without changing basal vascular parameters,[61,62] whereas sumatriptan reduced only the vasodilation induced by electrical stimulation.[17,60] One important advantage of olcegepant over the triptan family drugs is that it doesn't constrict the coronary arteries.[55,63,64]

Olcegepant has been shown to inhibit CGRP receptor in the trigeminal nucleus suggesting a similar central nervous system mechanism as well in treatment of migraine.[65] Another drug in this class, the MK-0974 (telcagepant) is another effective CGRP receptor antagonist when administered orally for the acute treatment of migraine.[66]

Both olcegepant (iv) in phase I, phase II and telcagepant (oral) in phase III have been used in migraine clinical trials.[66-69] The efficacy of the CGRP antagonists in the central modulation of pain in the hypothalamus has also been reported by Goadsby and colleagues.[5,70] A major side effect of these drugs is hepatic toxicity and elevated transaminase levels[71] although the presumably high doses of olcegepant and telcagepant alleviating the migraine symptoms are not so high after all.[72] A newer CGRP antagonist "BI44370TA" was reported to have a lower frequency of adverse effects in its phase II clinical trials.[73] It seems that the CGRP antagonists can act on CGRP receptors however it is uncertain whether they act on peripheral or central sites or both in migraine.[72]

Please see[74-77] for a comprehensive review on the CGRP and its functions, receptors, and the implication of CGRP-receptor antagonists as a novel approach in the treatment of migraine attacks. A recent report comparing the dose-response curve for the efficacy and adverse effect of several serotonin receptor ($5\text{-HT}_{1B/D}$) agonist drugs such as triptans or Lasmiditan (5-HT_{1F} antagonist) and the CGRP-receptor antagonists such as telcagepant, BI44370TA, MK-3207, and BMS-927711 indicates that the dose-response curve for efficacy of triptans is flat while their adverse effects increase by increasing the doses. While Lasmiditan and the CGRP-receptor antagonist drugs had also a flat dose-response curve, the efficacy-tolerability profile of the triptans is more favorable than others.[78]

Nevertheless, these newer drugs may have advantage in those patients that are triptan non-responders or with coronary heart disease or in patients with second rebound attack.[53,54,78] So far five different CGRP-receptor antagonist drugs with proof of efficacy have been used for the treatment of migraine but were discontinued due to hepatic toxicity and other side effects.[79-82]

Therefore, search for newer drugs against CGRP did not stop but this time, efforts were on developing antibodies against CGRP and it receptors.[83,84]

Monoclonal Antibodies against CGRP and its Receptor in the Treatment of Migraine Headaches

Antibodies against viruses have long considered as effective preventive methods in viral infections.[85,86] Antibodies against biological antigens (in this case, CGRP) can bind proteins and neutralize their effect (block the activity) whether being free in the circulation or membrane-bound and possibly intracellular proteins.

Monoclonal antibodies (mAbs) against CGRP and its receptors are newer drugs that have emerged in recent years[87] Table 1. Several investigators have been studying three mAbs for the prevention of episodic migraine and one mAb for the prevention of chronic migraine in the last couple of years.[87] The main idea was to remove the excess peripheral CGRP released from the perivascular nerve endings and for the anti-CGRP receptor antibodies to prevent the CGRP signalling cascade.[82,83]

Currently, three anti-CGRP mAbs have been developed that are in clinical trials. These include the LY2951742 (by Eli Lilly and Company), ALD-403 (by Alde Biopharmaceuticals) and TEV-48125 (LBR-101) developed by Teva Pharmaceuticals. The other class of mAb is against CGRP receptor complex, the AMG 334, developed by Amgen.

The ALD 403: Is a humanized Anti-CGRP mAb that has been used for episodic and chronic migraine, please see company's website.[88] It has completed phase 1[89-90] study and is in phase 2.[91] It has a half-life of approximately 31 days and has finalized positive proof-of-concept in phase 2a with a single i.v. dose of 1000 mg that can be repeated every 3-month.[92] The safety of the drug was assessed at 12 weeks after the infusion; the primary efficacy endpoint was observation of changes in the frequency of migraine days from the baseline to weeks 5-8 among adult patients age 18-55 years who had 9-10 days of headache per

ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-117

Drug: action	Dose; Half -life	Decrease in migraine days per month from baseline compared to placebo group	Reference
The ALD 403: mAb against CGRP	1000 mg per 3 month (single i.v.dose); Half-life: 31 days	5.6 in drug treated *versus* 4.6 days in placebo group (1 day difference) in the 3rd month.	92
LY2951742: mAb against CGRP	150 mg once every 2 weeks for 12 weeks (subcutaneous dose); Half-life: 28 days	4.2 in drug treated *versus* 3.0 days in placebo group (1.2 day difference in migraine headache) in the 3rd month.	94
TEV-48125: mAb against CGRP	0.2- 2000 mg (a one hour i.v. infusion) as a single dose once (on day 1), or up to 300 mg twice (day 1& 14); Half-life: 45 days Phase 2b clinical trials will use a 1-month run-in phase followed by one subcutaneous injection per month for 3 months	Still under investigation and analysis but reduction of both headache hours and days per month was reported.	82,104,105
AMG 334: CGRP-receptor mAb	Subcutaneous injection	Still under investigation and analysis but reduction in migraine days per month in episodic migraine patients was reported.	114,115

Table 1: Monoclonal antibodies (mAbs) used in clinical trials against CGRP or its receptor in the treatment of episodic and/or chronic migraine.

month where 8-9 of them qualified for migraine days.[82,92] Patients treated with ALD403 had a mean decrease of 5.6 migraine days between baseline and weeks 5-8 compared to the placebo group who had a decrease of 4.6 migraine days in the 3rd month (1 day difference).[82,92] The difference in the first month was 5.6 *versus* 3.9 days between the ALD403 group and the placebo (1.7 days difference).[82,92] These results showed the efficacy of ALD403 and there was no safety concern with the i.v. injection of 1000 mg of this mAb against CGRP.[92] Some side effects included infections of the upper respiratory, or urinary tracts, back pain, fatigue, nausea and vomiting that were seen in 57% of the 81 patients treated with ALD403 but were also seen in 52% of the 82 individuals who received the placebo treatment.[92]

LY2951742: Is another humanized anti-CGRP mAb (Lilly's clinical development pipeline)[93] with a half-life of 28 days[94] that has completed phase 1 clinical trials for the treatment of episodic and chronic migraine[95,96] and was tested in phase 2 clinical trials.[97] This phase 2 proof-of concept included randomized, double blind, placebo controlled investigations in 35 centres in the United States.[94]

The safety of the drug was assessed at 12 weeks treatment period after subcutaneous administration of 150 mg of this mAb twice per month (once every 2 weeks) for 12 weeks.[94] The primary endpoint was observation of changes in the number of migraine headache days per 28-day period that were evaluated at 9-12 weeks (although follow up assessment continued over 24 weeks as well) among adult patients age 18-65 years having 4-14 days of migraine headache per month.[94] Patients treated with LY2951742 had a mean decrease of 4.2 (62.5% decrease) migraine headache days between baseline and week 12 compared to the placebo group who had a decrease of 3 migraine days (42.3%).[94] This study indicated that LY2951742 may be beneficial in prevention of migraine.[94]

Adverse effects such as pain and erythema or both at the injection site (20% *versus* 6% in placebo group), upper respiratory tract infections (17% *versus* 9% in placebo group) and abdominal pain (6% *versus* 3% in placebo group) were more frequent in the LY2951742 treated group than the placebo treated group.[94] Another effort was also determining the dose selection for phase 2 studies.[98] LY2951742 is currently in clinical trial phase 3 for treatment of episodic cluster headache.[99]

TEV-48125: Also known as LBR-101 (with a former identity: RN-307) is also a humanized anti-CGRP mAb for treatment of episodic and chronic migraine (Teva Pharmaceutical Industries Ltd.)[100] and has a half-life of about 45 days, the longest among the anti-CGRP mAbs.[101] Its safety profiles were demonstrated through six phase one studies.[102] Studies in monkeys established the safety and tolerability of LBR-101 and appeared to have no significant effect in cardiovascular and haemodynamic parameters.[103] Clinical studies used 0.2-2000 mg given as a single dose (a one hour i.v. infusion) once (on day 1), or up to 300 mg given twice (day 1 and day 14) to human subjects.[104] These doses were well tolerated and overt safety concerns were not noticed.[82] TEV-48125 is currently in two phase 2b clinical trials, administered as a 1-month run-in phase followed by randomization and monthly subcutaneously injections for 3 months.[82] TEVA company announced the successful completion a phase 2b clinical trial using TEV-48125, meeting the primary and secondary endpoints in both chronic and episodic migraine study after a single dose injection which was significantly higher than placebo and resulted in significant reduction of both the number of monthly cumulative headache hours, and the number of headache days of at least moderate severity relative to baseline.[105] No significant cardiovascular or liver function adverse effects were seen compared to the placebo receiving control group, please see[82,104] for details of the studies and a comprehensive review.

AMG 334: Is a CGRP-receptor mAb, indicated in Amgen media news release[106] that has completed phase 1[107-109] and is in its phase 2 clinical trials.[110-112] A few recent reports[113] and those of Amgen

released results (reported by PRNewswire) of a global phase 2 clinical trial (which was also presented in the 17th congress of the International Headache Society, Valencia, Spain) indicate that this fully human mAb, the AMG 334 seems to have significantly decreased the mean migraine days per month in episodic migraine patients.[114,115] These studies are currently ongoing but please see references[112,113] for more details of AMG 334 studies that has been released so far.

Biological Role of CGRP in Homeostasis

So far we discussed the CGRP being a neurotransmitter/neuromodulator that mediates vasodilation peripherally and acting on its receptor on central neurons but it is important to discuss some other biological roles of CGRP in the body.

In the lung and respiratory airways, in addition to CGRP expression of the sensory neurons innervating the airways, blood vessels and lymphoid tissue,[116] CGRP is also localized in specialized epithelial (neuroendocrine) cells in the lungs and is involved in regulation of vascular tone,[117] protection of the bronchial tree, the anti-inflammatory responses and tissue repair.[118] Ablation of sensory nerve fibers leads to a significant increase in inflammatory responses, and congenital CGRP-knockout mice have increased reperfusion-induced tissue inflammatory activities.[119] In the gastrointestinal (GI) tract, stimulation of sensory nerves reduces reperfusion-induced liver injury and stressed-induced gastric mucosal injury in rodents presumably by CGRP-induced increase in the expression of prostacyclin [PGI(2)] and attenuation of inflammatory responses such as tissue Tumor Necrosis Factor (TNF) increase and tissue accumulation of neutrophils.[119]

CGRP is a negative regulator of innate immune responses by inhibiting the antigen presenting cells such as macrophages and dendritic cells, blocking their capacity to produce proinflammatory cytokines.[120,121] This effect of CGRP is mediated by production of Interleukin-10 (IL-10) and IL-10 independent processes that stimulate the expression of the inducible cAMP early repressor (International Confederation of Energy Regulators (ICER)) and inhibition of NF-$_{K}$B, although in sepsis this effect of CGRP may complicate the situation.[121] A central role for intestinal dendritic cells in neuroimmune communication and similar roles for neuropeptides including CGRP in the skin, lung and GI tract has also been proposed.[122]

The Toll-like receptor 4 (TLR4), a bacterial gram negative receptor, can activate the Vanilloid receptor 1 (transient receptor potential action channel subfamily V member 1, TRPV1) and result in the release of CGRP and its anti-inflammatory effects in the intestine.[123]

CGRP expressing nerve fibers in the GI tract are involved in pain, GI motility and secretion, defense against irritants, and wound healing of ulceration, presumably acting *via* TRPV1 receptor.[124] The central action of CGRP controls the GI motor function and intestinal motility including the migrating motor complexes.[125]

CGRP and TRPV1 (and some other neuropeptides and receptors/channels) are also involved in the neural plasticity of almost all parts of GI tract including the liver and pancreas during pathological conditions.[126]

CGRP release from the mesenteric perivascular nerve fibers increases the induction of pannexin-1-formed channel opening (hemichannels) which results in reduction of pannexin-1 and endothelial Nitric Oxide Synthase (eNOS) expression, and CGRP blockade increases the eNOS expression significantly.[127] These channels are important in the regulation of blood brain barrier as well.

There are evidences that CGRP expressing fibers of trigeminal ganglion innervate the pineal gland in several mammalian species.[128] Pineal gland is known to regulate hypothalamus, the command center for the control of autonomic and endocrine activities. Although this might be involved in the autonomic responses of pain following activation of the trigeminovascular system.

There is even a role for CGRP in the neuromuscular transmission. CGRP seems to significantly stimulate the calcium (Ca^{++}) channels at the sarcoplasmic reticulum leading to Ca^{++} release into the cytosol of the skeletal muscle and also stimulate the Ca^{++} channels at the sarcolemma to a lesser extent.[129]

CGRP expression increases in injured motor neurons and is believed to activate neuroglial cells such as astrocytes and microglial cells in the CNS which is believed to be responsible for tissue remodeling and repair.[52]

DISCUSSION

Several anti-migraine drugs have been developed in the past three decades. Tremendous efforts by brave scientists, clinicians, drug companies, and patients (for clinical trials) in this field has contributed to the significant achievements so far and this effort continues until various treatment options for migraine are found.

Although CGRP has several important roles in human body, increases in its levels in the blood of migraine patients has been linked with the headache. Therefore, inhibiting its activities by means of CGRP-receptor antagonists and/or monoclonal antibodies against CGRP or its receptor has been a focus of more than a decade of research to find another alternative treatment to alleviate the pain of migraine specially on those who are non-respondent to other drugs and also find a more convenient type of medication that patients could take once a month or so and become pain free.

ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-117

Anti-CGRP treatment strategy is one of the alternative therapies to a number of drug treatment options currently available for the prophylaxis and treatment of headache in migraine. Currently, the first choice treatment options of migraine include the use of triptan [serotonin (5-$HT_{1B/D}$)] receptor agonist family drugs and NSAIDs. A number of prophylactic drugs such as the Antiepileptic drugs (AEDs), betablockers, and Ca^{2+} channel blockers are currently being used to treat migraine. These are in addition to some other drugs and non-drug treatment options that are currently available to treat migraine headache. Nevertheless, research in the treatment of migraine is always looking for newer and more convenient, more efficient and more potent drugs or treatment strategies with fewer or no adverse effects.

Although promising, the CGRP-receptor antagonist drugs (the "gepant" family) were discontinued due to their side effects, especially the hepatotoxicity. Several other CGRP receptor antagonists such as MK-3207, BI 44370, BMS-846372 are still in clinical trials, please see[77] for review. Search for newer anti-CGRP compounds with sufficient efficacy and less or no adverse effects continued in recent years.

It seems that blocking CGRP or its receptor alleviates the headache in migraine patients. A number of studies so far in phase one and phase 2, using mAbs against CGRP or its receptors have shown a decrease in the number of headache days per month while did not have a significant adverse effect although these studies are still ongoing at the moment. One important fact about CGRP mAbs is their half-life (and their clearance from the body) which is in the range of a few weeks. This is very good and convenient for migraine patients since with one injection or so per month they experience much less headache days per month although the clearance time of the mAbs from the body is also extended equally.

If proven effective with minimal or no significant adverse events after completing the clinical trials, mAbs against CGRP or its receptors will be another revolution like the triptan family drugs in the field of migraine treatment and will increase our abilities and options to treat migraine effectively. Some of the adverse events of mAbs against CGRP such as infections and abdominal pain seen in some patients may correspond to decrease or inhibition of biological activities of CGRP or activation of some other compensatory mechanisms. Therefore, long term use and monitoring of the patients would add more knowledge to our current understanding.

Such mAbs will certainly be beneficial in other painful or other conditions if their pathophysiology is similar.[130] CGRP is among the four neuropeptides that were increased in the archived neonatal blood of infants who were later (after couple of years) diagnosed having Autism Spectrum Disorders (ASD) or mental retardation.[131]

It is not known why some neuropeptides are increased in ASD, but increased blood serotonin levels has been linked to loss of brain serotoninergic terminals *via* a negative feedback, disrupting the serotonin function leading to a compensatory increase in CGRP level in ASD patients.[132-134] Although, several genes have been implicated in ASD[135] environmental factors including GI abnormalities and immune imbalance might play a role in ASD[136] and other psychological health problems.

The role of CGRP increase in ASD children is not very well known but both serotonin and CGRP are involved here as well. Some GI problems including diarrhea and abdominal pain in autistic children[136-139] are due to various causes but the exact pathomechanism of GI problems in ASD children is not completely understood.[140] It is however possible that anxiety, sensory over-responsivity and GI problems are interrelated phenomena in children with ASD.[141]

Several studies using CGRP knockout mice or other related studies have reported about the various roles of CGRP in pathological conditions in animal studies and results are indicative of some protective and some deleterious effects of CGRP in neuroprotection, immune activation or vascular structure and function.[142-150]

However, mAbs against CGRP in migraine treatment research should tell us more about the long term effect of CGRP inhibition.

Interestingly, inhibiting the TRPV1 receptor or interfering with CGRP activity may improve health and increase age longevity as shown in a recent study in mice[151] and brought the ideas of "die another day"[152] and "a long pain-free life".[153]

Can mAbs against CGRP increase our longevity?

CONFLICTS OF INTEREST

This paper has been written without external financial funding. There is no conflicts of interest.

ACKNOWLEDGMENTS

The author's salary is paid by the University of Central Florida, Orlando, FL, USA.

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ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-118

Mini Review

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Volume 2 : Issue 3
Article Ref. #: 1000NOJ2118

Article History:
Received: September 5th, 2015
Accepted: October 12th, 2015
Published: October 13th, 2015

Citation:
Ochoa V, Loeffler AJ, Fowler CD. Emerging role of the cerebrospinal fluid – neuronal interface in neuropathology. *Neuro Open J*. 2015; 2(3): 92-98.

Emerging Role of the Cerebrospinal Fluid – Neuronal Interface in Neuropathology

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ABSTRACT

The choroid plexus and cerebrospinal fluid have recently begun to emerge as essential regulators of neural function. Factors produced by the choroid plexus are released into the ventricular environment and thus provide a rich source of extracellular signaling molecules throughout the central nervous system. Identified factors in the cerebrospinal fluid include growth factors, hormones, proteins, peptides, lipids, glucose, microRNAs (miRNAs), messenger RNA (mRNA), and enzymes. In addition to mediating neural function, these factors have the potential to serve as biomarkers of disease states. In this review, we highlight recent advances demonstrating the importance of extracellular signaling mechanisms in mediating neural function and provide recent evidence for their role in neuropathology.

KEYWORDS: Choroid plexus; Cerebrospinal fluid; Microvesicles; Extracellular communication; Neuropathology.

ABBREVIATIONS: CSF: Cerebrospinal fluid; siRNA: short-interfering RNA; mRNA: messenger RNA; miRNAs: microRNAs; MVEs: Multivesicle endosomes; IGF2: Insulin-like growth factor 2; FGF2: Fibroblast growth factor 2; FXTAS: Fragile X-associated tremor/ataxia syndrome; AIDS: Acquired Immune Deficiency Syndrome.

INTRODUCTION

Historically, the function of the Cerebrospinal fluid (CSF) was considered to be limited to maintenance of extracellular ion concentrations and to serve as a protective 'cushion' during cranial impact. However, recent advances have revealed that the CSF provides a rich source of signaling molecules, including growth factors, hormones, proteins, peptides, lipids, glucose, microRNAs, mRNA, and enzymes.[1-5] Indeed, primary CSF removed from the brain is sufficient to maintain cortical explants and cells in culture without the presence of other factors,[6] clearly demonstrating the extent of micronutrient and growth factor enrichment in this fluid. Several initial studies of CSF function had suggested that signaling factors present in the CSF mediate satiety, circadian rhythms, and locomotor behavior.[7,8] In these early studies, reinstatement of feeding behaviour was induced by infusing CSF collected from fasted sheep into the ventricles of satiated sheep,[9] and similarly, CSF collected from sleep-deprived goats increased the duration of sleep and decreased locomotor activity when infused into the ventricles of rats.[7] These findings indicated that substances present in the CSF can exert a significant influence on motivated behaviors. More recently, Pedrazzoli and colleagues established that the peptide orexin (a.k.a., hypocretin) is increased in the CSF during sleep deprivation.[10] In addition to regulating arousal and wakefulness, orexin has been implicated in drug reinforcement, obesity and neurodegenerative diseases, such as Parkinson and Alzheimer's diseases.[11-15] As such altered expression of orexin in the CSF under these physiological conditions could be a mediating factor for the sleep-related effects in the earlier study[7] and may also have additional multifaceted effects on physiological function.

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CHOROID PLEXUS AND CEREBROSPINAL FLUID (CSF)

In vivo, production of CSF occurs at several choroid plexus sites, including the lateral, third and fourth ventricles, thus creating an independent circulatory system for the brain.[3] At each of these sites, the choroid plexus appears to differ in some respects in structure, function, and factors produced/released into the ventricles.[16] The epithelial cells that comprise the choroid plexus contain extensive basolateral infoldings and microvilli, providing an extensive surface area for transport into the ventricular fluid. These cuboidal epithelial cells exhibit a polarized shape, with differential function ascribed to the apical and basolateral membranes.[17] The apical membrane interfaces with the capillaries of the brain and mainly functions to uptake nutrients from the blood, whereas the basolateral membrane provides a removal mechanism for toxins and excess substances from the CSF, in addition to releasing factors into ventricular circulation.[17] As such, dysfunction in the transport mechanism of the choroid plexus could potentially alter CSF compositions and compromise brain health.

The potential for CSF-derived factors to impact neural function may be further imparted when one takes into account that the total surface area at the choroid plexus-CSF interface is roughly the same as the entire blood-brain-barrier.[16] As CSF is generated, it moves transcellularly and paracellulary among the epithelial cells of the choroid plexus to be released into the ventricular space.[16] Since the amount of CSF produced allows for turnover of approximately four times per day in humans,[18] the levels of circulating factors has the potential to be continuously regulated to influence neuronal function. It has also been proposed that the apical membrane of the choroid plexus expresses receptors that function as feedback loops to mediate the further release of certain factors into the ventricles,[16] and thus the presence of growth factors, neuropeptides, proteins, cytokines and hormones may be regulated in this manner. Indeed, this feature of the choroid plexus has been experimentally exploited to alter growth factor release; genetically displaying growth factor ligands on bacteriophage coats binds the construct to receptors on the choroid plexus cell surface, thus altering further release of the growth factor into the ventricle.[19] In addition to factors produced by the epithelial cells of the choroid plexus, the presence of blood vessels in the choroidal stroma allows for the presence of the CSF-blood interface through which factors from the blood may enter the central nervous system through leaky endothelial junctions.

EXTRACELLULAR TRANSPORT IN THE CSF

It has been proposed that the transport of factors from the choroid plexus into the ventricular CSF may occur *via* three main routes: (1) transport in the CSF itself as the choroid plexus is permeable for smaller molecules, (2) membrane-bound transport mechanisms on the plasma membrane of choroidal epithelial cells, (3) release from the intracellular compartment as extracellular vesicles[20] (Figure 1). In the prior literature, these extracellular vesicles have been referred to as either exosomes or microvesicles, although this terminology inconsistently varies across fields.[21] Van der Pol and colleagues propose that the main distinction between the two types of vesicles concerns their size, with exosomes being smaller in diameter than microvesicles when examined from the same cell. However, this distinction is not clearly defined when one considers varying types of cells. For instance, exosomes have been most commonly reported to range from ~50-100 nm in diameter, and microvesicles from between ~20-1000 nm in diameter; as can be seen, these classifications provide a range of overlap.[21] Both types of extracellular vesicles can be formed by an outward blebbing of a cell's plasma mem-

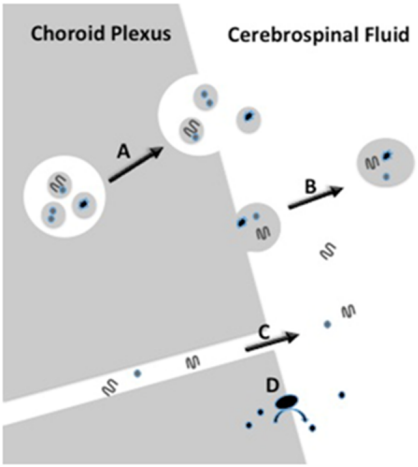

Figure 1: Mechanisms of extracellular transport from the choroid plexus into the cerebrospinal fluid. Factors derived from the choroid plexus may be released into the ventricular space: (A) as exosomes released from intracellular Multivesicle endosomes (MVEs) through exocytosis, (B) *via* blebbing of the cellular membrane as a microvesicle or exosome, (C) transcellularly and/or paracellulary with release of cerebrospinal fluid, or (D) *via* membrane-bound transport mechanisms located in the epithelial plasma membrane.

ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-118

brane, but exosomes may be additionally formed as intraluminal vesicles within multivesicle endosomes that are then released from the cell as the endosome fuses with the plasma membrane. For the purposes of this review, we will employ the general terminology of extracellular vesicles to refer to both exosomes and microvesicles, and moreover, it should also be noted that this classification is distinct from membrane particles or apoptotic vesicles.[21] Many cell types have been shown to release extracellular vesicles *via* budding of the cell membrane, including epithelial, immune, tumor and stem cells,[22,23] and the resulting vesicles differ in content and function. Whereas initial investigations assumed extracellular vesicles contained cellular debris, growing evidence has established that these compartments are enriched with a vast source of signaling molecules that have crucial roles in a number of physiological processes. Release of extracellular vesicles has been shown to occur *via* Ca2+-, protein kinase C-, or ceramide-dependent mechanisms, and after entry into the CSF, the vesicles may immediately breakdown to dump contents into the fluid or can travel to a distant site to fuse with the membrane of a target cell and transfer genomic material.[22-24] The method of vesicular packaging for extracellular communication may be preferred for mRNA and miRNAs transport, as exposure to circulating RNAses are limited and long-distance communication may be achieved *via* cell-specific targeting motifs on the vesicle surface. Importantly, several recent reports have demonstrated that mRNA from microvesicles can become integrated and translated into the proper protein within the target cell,[23,24] short-interfering RNA (siRNA) packaged into exosomes can efficiently silence gene expression,[25] and epigenetic changes can be induced in target cells *via* transfer of miRNAs.[22] In consideration of these findings, elucidation of the structure and function of these packaged compartments could hold promise as a novel avenue for therapeutic delivery of preloaded vesicles with mRNA, miRNA, siRNA or pharmacological compounds into the central nervous system.

RELEVANCE TO NEUROPATHOLOGY

With the exception of hydrocephalus, the CSF has not traditionally been considered a vital regulatory mechanism of and/or implicated in human disease states. However, recent reports are beginning to redefine our understanding of choroid plexus and CSF function as they demonstrate the importance of factors derived from the CSF in maintaining physiological function (Table 1). For instance, growth factors produced by the choroid plexus, such as Insulin-like growth factor 2 (IGF2) and Fibroblast growth factor 2 (FGF2), have been shown to regulate neurogenesis throughout the lifespan.[3,6] Further, an elegant study from Sawamoto and colleagues recently demonstrated that the CSF directly interacts with cilia in the subventricular zone to mediate the migration of progenitor cells in the adult brain.[26]

Choroid plexus transport has been implicated as a contributing factor for certain neurodegenerative diseases. For instance, Fragile X-associated tremor/ataxia syndrome (FXTAS) is associated with iron dysregulation in mitochondria.[27] Interestingly, post-mortem FXTAS subjects exhibit an accumulation of iron in the stroma of the choroid plexus and decreased amounts of transferrin, ferroportin, and ceruloplasmin, all of which are essential to the transport of iron.[27] These findings suggest that abnormal transport of iron within the choroid plexus may contribute to pathophysiology exhibited by FXTAS subjects. Another disorder, cerebral folate transport deficiency, is characterized by a lack of B-vitamin within the brain. The polarized cells of the choroid plexus have been shown to translocate the folate receptor α(FRα) in a unilateral direction from the basolateral to the apical compartments, leading to exocytosis into the CSF and subsequent integration in the brain parenchyma.[28] Thus, abnormal transport of substrates involved in the production of B-vitamins may underlie the pathology found in this disorder.

To date, dysfunction of the choroid plexus has been most studied as a mediating factor of Alzheimer's disease. Postmortem, neural pathology in the Alzheimer's brain is evidenced by a build-up of amyloid-β (Aβ) plaques and intracellular neurofibrillary degeneration of hyperphosphorylated tau (neurofibrillary tangles).[29,30] Under normal circumstances, the Aβ protein is produced by the brain and subsequently becomes cleared through enzymatic degradation, capillary reabsorption, and/or CSF transport through the choroid plexus.[29,31] In contrast, pathological accumulation of Aβ plaques and neurofibrillary tangles in the disease state leads to dysfunction of neurons and synapses throughout the brain, most notably those in brain regions involved in memory and cognitive function, such as the hippocampus and cortex.[32] As such, recent evidence suggests that the choroid plexus and CSF may play a significant role in the pathology of Alzheimer's disease.[1,31,33] Altered clearance of Aβ by the CSF with aging results in accumulation of Aβ protein, thus promoting the formation of plaques. In late onset Alzheimer's disease, structural abnormalities of the choroid plexus, which in-

Disease	Fragile X-Associated Tremor/Ataxia Syndrome	Cerebral Folate Transport Deficiency	Alzheimer's Disease	Multiple Sclerosis	AIDS
Choroid Plexus Characteristics	Iron accumulation in stroma	Failure to transport FRα along with B-vitamin	Failure to clear amyloid-β (Aβ) plaques	HLA-DR expression	Accumulation of HIV-1
CSF Characteristics	Low iron levels	Low FRα and B-vitamin levels	Accumulation of amyloid-β (Aβ) protein	Increased CD4/CD8 ratio	To be further investigated

Table 1: Summary of neuropathology associated with abnormal choroid plexus and CSF.

clude cellular atrophy, calcification and fibrosis, and thickening of the basement membrane,[29] are evidenced. These abnormalities are thought to lead to altered synthesis, secretion, clearance and transport of factors between the choroid plexus, cerebrospinal fluid and blood.[29] Therefore, in patients with Alzheimer's disease, choroidal dysfunction prevents adequate clearing of Aβ from the CSF and promotes Aβ accumulation in the brain.[29,33] Another possible role for CSF in the pathogenesis of Alzheimer's disease is through transport of melatonin. The pineal gland directly secretes melatonin into the CSF of the third ventricle,[34] or, alternatively, the hormone may enter *via* leaky endothelial cells of blood vessels in the choroid plexus.[35] Interestingly, recent findings suggest that the amount of melatonin in the CSF is negatively correlated with the status of Alzheimer's disease symptoms.[36] Through its actions as an antioxidant it has been proposed that melatonin exerts neuroprotective effects by counteracting oxidative damage.[36] In the younger brain, evidence suggests that melatonin administration can result in anti-amyloid and antioxidant effects; however, administration of melatonin to the aged brain has been shown to exert a minimal effect on pre-existing amyloid deposits.[37] Thus, as a therapeutic approach, strategies to increase melatonin in the CSF may be of benefit in the early stages of Alzheimer's disease and/or as a preventative measure based on familial considerations.[38]

The choroid plexus also functions as a principal mediator of the innate immune response of the central nervous system. Peripheral immune molecules interact with receptors located on choroid plexus cells to initiate the release of proinflammatory molecules, such as interleukins, into the CSF.[16] Myeloid progenitors located in the vascularized choroid stroma have also been shown to provide a source of brain macrophages.[39,40] Moreover, inflammatory processes mediated by the choroid plexus have been speculated to contribute to the heightened immune response found in multiple sclerosis and encephalitis.[41] In addition, the choroid plexus is a main entry point for viruses to infiltrate the brain from the periphery. For instance, the presence of HIV-1 in the choroid plexus has been suggested to occur prior to the onset of Acquired Immune Deficiency Syndrome (AIDS) and immunosuppression,[42] and infected CSF or choroid plexus-derived macrophages can induce toxic effects on neurons *in vitro*.[43] HIV-1 or other viruses may also be capable of altering the expression of signaling molecules within the epithelial cells of the choroid plexus to permit enhanced entry of the virus into the CSF, a possibility which needs to be more systematically investigated in future studies.

Finally, given the close proximity of CSF to brain regions implicated in substance abuse, such as the habenula, hippocampus, and interpeduncular nucleus,[44,45] signaling molecules in the CSF could potentially regulate the neural processes underlying the addictive state. Interestingly, nicotine has been shown to mediate the function of the choroid plexus.[46,47] Transthyretin, the plasma thyroid hormone transport protein, is produced by the choroid plexus and acts to transport thyoxine across the blood-brain barrier,[48] and nicotine administration has been found to increase the synthesis and release of transthyretin into the CSF.[47] Further, prenatal exposure to nicotine has also been correlated with an increased incidence of pathological features of the fourth ventricle choroid plexus and premature death.[46] However, further investigations will be critical to ascertain whether extracellular factors from the choroid plexus/CSF are important mechanisms that mediate the development and maintenance of drug dependence. "If established, these findings have the potential to redefine our understanding of novel signaling mechanisms within the brain and in doing so, could provide a foundation for more efficacious therapeutic approaches Table 1."

CONCLUSION

Our current understanding of the function of the choroid plexus and CSF has begun to be transformed, and as such, the emerging importance of these signaling mechanisms must now be recognized as putative essential mediators of brain function. Extracellular signaling factors have been shown to integrate in and modulate function of neurons within the brain and thus, have the potential to both maintain normal homeostatic function and/or contribute to pathological disease states. Moreover, CSF-derived factors also hold the potential to serve as biomarkers of disease. As the field progresses, the vital function of factors derived from the choroid plexus will likely continue to emerge, and these advances may then provide a foundation for novel approaches to treat neuropathology in humans.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

ACKNOWLEDGEMENTS

This work was supported by grants from the NIH National Institute on Drug Abuse (DA039658&DA032543 to C.D.F.).

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ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-119

Mini Review

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Volume 2 : Issue 3
Article Ref. #: 1000NOJ2119

Article History:
Received: November 11th, 2015
Accepted: December 14th, 2015
Published: December 15th, 2015

Citation:
Adigo AMY, Adambounou K, Agbotsou IK, Agoda-Koussema LK, Adjénou KV. Neurovascular conflicts of cerebellopontine angle: a review of the literature. *Neuro Open J.* 2015; 2(3): 99-105.

Neurovascular Conflicts of Cerebellopontine Angle: A Review of the Literature

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ABSTRACT

The pathology of the cistern of the cerebellopontine angle is primarily the disease of the nervous and vascular structures that it contains and of the meninges that line it. It appears by the Trigeminal Neuralgia (TN), Hemifacial spasm (HFS), and Glossopharyngeal Neuralgia (GN). We have reviewed the anatomy, pathogenesis, diagnostics and therapy of neurovascular conflicts of cerebellopontine angle. The clinical manifestations of the conflict vary according to the affected nerve. The diagnosis is made on the basis of symptoms but need to be confirmed by imaging. Now-a-days, high-fields Magnetic Resonance Imagings (MRIs) are the standard gold diagnostic method but stay impervious in areas or countries that are less medically equipped. The treatment of neurovascular conflicts of cerebellopontine angle is conservative or interventional. The interventional acts constitute the only curative treatments.

KEYWORDS: Neurovascular conflict; Cerebellopontine angle; Glossopharyngeal neuralgia; Trigeminal neuralgia; Hemifacial spasm.

ABBREVIATIONS: CPA: Cerebellopontine angle; TN: Trigeminal Neuralgia; GN: Glossopharyngeal Neuralgia; HFS: Hemifacial spasm; REZ: Root Exit Zone; MRI: Magnetic Resonance Imaging; PICA: Posterior Inferior Cerebellar Artery; AICA: Anterior Inferior Cerebellar Artery; VA: Vertebral Artery; APC: Anterior Piriform Cortex; MeSH: Medical Subject Headings.

INTRODUCTION

The pathology of the cistern of the Cerebellopontine angle (CPA) is primarily the disease of the nervous and vascular structures that it contains and of the meninges that line it. Knowledge of its anatomy and pathogenesis makes it possible to understand and search for a rare pathology, including Trigeminal Neuralgia (TN), Hemifacial spasm (HFS), and Glossopharyngeal Neuralgia (GN). Trigeminal neuralgia consists of brief paroxysms of pain in the facial distribution of the trigeminal nerve, precipitated by stimuli to sensory endings in the trigeminal receptive area.[1] The overall incidence is estimated to be approximately 3-5 cases per year per 100,000 people and increases with age.[2] HFS is a facial movement disorder characterized by involuntary, unilateral and intermittent twitching of muscles innervated by the facial nerve.[3] Like in TN, in more than 95% of the cases HFS is caused by neurovascular compression affecting the Root Exit Zone (REZ) of the facial nerve. Medical imagery, based on the Magnetic Resonance Imaging (MRI), is systematic and enables us to preview the conflict. We have reviewed the anatomy, pathogenesis, diagnostics and therapy of neurovascular conflicts of cerebellopontine angle.

METHODS

The research for this review was data mining through Medline and Google scholar web

ISSN 2377-1607 Open Journal http://dx.doi.org/10.17140/NOJ-2-119

sites. The Medical Subject Headings (MeSH) terms were "neurovascular conflict", "cerebellopontine angle", "glossopharyngeal neuralgia", "trigeminal neuralgia" and "hemifacial spasm". The research included English, French and Russian studies in humans. Articles were included when dealing with anatomy, pathology, pathogenesis, diagnostics or therapy of neurovascular conflicts of CPA. Case series and single cases were included. Articles were excluded when the cause of the conflict were non-neurovascular. Bibliographies of selected articles were screened for additional relevant articles. We used HITACHI (AIRIS Vento) 0,3T. The sequences carried out were: 3DT1, 3DT2 with high resolution and angio-MR-3DTOF. Informed consent was obtained for patients to publish their pictures.

ANATOMICAL RECALL

The CPA is located between the superior and inferior limbs of the cerebellopontine fissure, a V-shaped angular cleft, formed by the cerebellum folding around the pons and middle cerebellar peduncle.[4-6] The CPA faces the posterior surface of the temporal bone. The middle cerebellar peduncle fills the interval between the superior and inferior limbs of the angle (fissure). The apex of the angle is located laterally where the superior and inferior limbs meet. The fourth through the eleventh cranial nerves are located near or within the angular space between the two limbs.[7]

The surgical cerebello pontine angle (CPA) can then be divided into three spaces comprising each one a nerve, vessels and its distinct pathologies:

- Space of the mixed nerves, inferior external occupied by the mixed nerves IX, X and XI after passing through the jugular foramen. Apart from these, the sigmoid sinus will become gulf of the chin-strap. The artery belonging to this territory is the Posterior Inferior Cerebellar Artery (PICA) born from the ipsilateral vertebral artery;[7-9]
- Space located coarsely at the medium of the CPA, more internal than the previous, consists of the acousticofacial package (VII and VIII), emanating from the bulbo-protuberantial furrow and engulfing themselves in the porus. It crosses this space in straight line. It is the zone of the Anterior Inferior Cerebellar Artery (AICA) which may form several loops there engaging itself or engaging one of its branches towards the porus and more or less deeply in the meatus. In this space, the presence of a vein is very variable from one subject to another, but one can find with the former face of the cerebellum and sometimes joining directly the petrous sinus, a vein of rather large gauge;[7-9]
- Third space is located at the anterior tip of the Cerebellopontine space, well inside of the precedent. It contains the motor and sensitive roots of the Trigeminal nerve or the fifth cranial nerve (CN V) which, being born from the former face of the protuberance, will join the trigeminal cavum. The other occupying permanent structure of this space is the vein of Dandy, very bulky vein joining the higher petrous sinus. The artery of this territory is the superior cerebellar artery which may often form a loop by contacting the trigeminal nerve.[7-9]

PATHOLOGY AND PATHOGENESIS

The vertebro-basilar arterial system is never perfectly symmetrical: the unilateral Vertebral Artery (VA) is all the more bulky as its counterpart contralateral hypoplastic. The basilar artery can be also very tortuous. Thus, these large arterial trunks or their branches can come in contact with the various nervous structures of the CPA and produce there a mechanical aggression on both peripheral and central nervous tissues[10] leading to various signs and symptoms of neuralgias. The "ephaptic" theory refers to the development of a true short-circuit electric activity that may occur by time between fibers constituting the nerve.[10] Similarly, a hyper reactivity at the core of the cranial nerves in the brainstem known as the "nuclear" theory[10] may cause the sign and symptoms of these disorders. Nevertheless, there is another unifying theory, the Kindling effect, which says that a central hyper excitability of the cranial nerves does not exclude an associated peripheral origin.[10] In the three cases, the "electric discharges" thus produced are responsible for various pathologies which are, by order of frequency: neuralgia of the trigeminal nerve and the spasm of the hemi face. In 95% of the cases, there is an arterial loop. The seat of the conflict is the REZ (zone of central transition myelin – myelin peripheral) of variable situation from one nerve to another. It seems that smallness of the cisterns of the Anterior Piriform Cortex (APC) and short trigeminal nerve have an impact on the pathogenesis of the essential neuralgia by facilitating the neuro-vascular conflict, particularly among younger patients.[11]

The major etiology of cerebellopontine neurovascular conflict is the pulsatile compression of a vascular structure within a few millimeters from the origin of the nerve (REZ). Persistence of the phenomenon leads to demyelination of the nerve.[12] Baliazina, has shown that the contact between the superior cerebellar artery and trigeminal nerve trunk cannot lead to the development of trigeminal neuralgia since traumatizing action on the nerve results not from the pulsation of the wall of artery which touches the nerve, but from the strokes of the distal arm of superior cerebellar artery loop, that unbends during each systole and is located at an angle to trigeminal nerve trunk.[13]

The vessels responsible for the conflict vary according to the reached nerve. The most common offending vessel in the Hemifacial spasm (HFS), is the AICA accounting for more than 50% of the cases, while the rest may be caused by the PICA, the basilar artery or veins.[14] HFS caused by developmental venous anomaly is a very rare occurrence. Developmental venous anomaly is the most frequently found cerebral vascular malformation constituting approximately 60% of all vascular lesions.[15,16] The

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role of hypertension in the late onset of HFS have been shown in a family, spanning four generations, using MRI and magnetic resonance angiography.[17] Figures 1 and 2 show respective normal MRI of the cranial nerves VII and V.

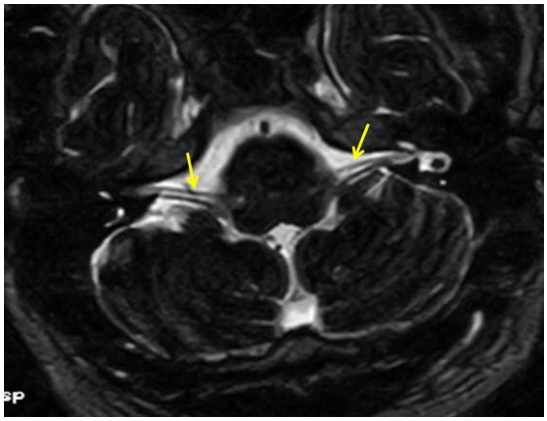

Figure 1: MRI aspect, axial sequence 3DT2 showing a normal nerve VII (yellow arrow).

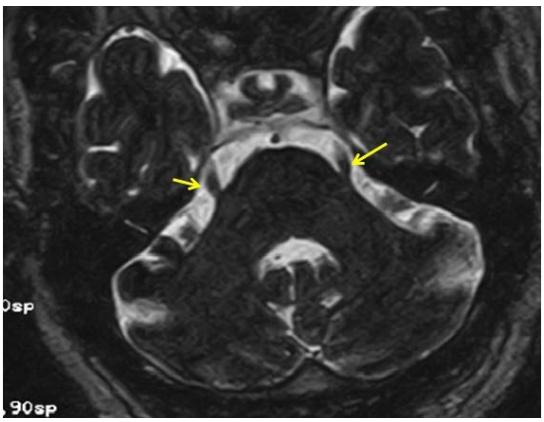

Figure 2: MRI aspect, axial sequence 3DT2 showing a normal nerve V (yellow arrow).

The vessels which most frequently make contact with a trigeminal nerve are the superior cerebellar artery (55-88%), then the AICA, and, in various order, depending on the author, the basilar artery, PICA or a vein embedded in the nerve.[18,19] Sometimes more than one vessel contacts with the nerve. Some authors think that the offending vessel should dislocate the nerve, while according to others it is enough to find a contact between them.[18,20] Furthermore, the vessel should touch the nerve at a right or acute angle at the level of the REZ, which means up to 6 mm from the point of sensory root exit from the pons.[21]

CLINICAL MANIFESTATION OF TN, HFS AND GN

TN is recognized by unilateral short-lived, strong, sharp, shooting pains in one or more branches of the fifth cranial nerve. The description of the pain is very important; it must be sharp, shooting, lancinating, and "electric shock". The pain can be brought on by ordinary stimuli, such as eating, washing, shaving, cold, warmth, and draught.[22]

HFS is a facial movement disorder characterized by involuntary, unilateral and intermittent twitching of muscles innervated by the facial nerve.[3] The literature describes the frequency of site of onset: the orbicularis oculi muscle in 90%, the cheek in 11% and the perioral region in 10% of cases. Over months to years, the spasms spread gradually to other muscles innervated by the ipsilateral facial nerve. Tonic spasm is generally accompanied by twitching and synkinesis.[23]

GN is characterized by paroxysms of repetitive lancinating pain localized unilaterally in the tongue, soft palate, and throat in the lateral and posterior parts of the pharynx, and radiating to the ipsilateral ear. Neuralgia can be triggered by swallowing, coughing, yawning or chewing, and usually lasts seconds or minutes. Vagoglossopharyngeal neuralgia is a very rare type of GN associated with cardiac syncope, arrest and bradycardia caused by vasodepressor reaction of the vagus nerve. Vagoglossopharyngeal neuralgia occurred in only 4 of 217 patients with GN.[24,25]

IMAGING STUDIES IN TN, HFS AND GN

When the diagnosis of neurovascular conflicts of CPA is made, the patient needs to undergo a MRI scan to exclude specific pathologies such as a tumor or multiple sclerosis, which could cause a secondary TN, HFS or GN. The MRI scan can also be used if there is a suspected compression of the nerve in the posterior cranial fossa. Sometimes the MRI scan is sensitive enough to detect blood vessels that have come in contact with the nerve. Now-a-days, the high MRI fields became inescapable in the diagnosis of neurovascular conflicts of the CPA.[26-29] However, in areas or countries that are less medically equipped, certain authors think that the low-fields MRI can constitute an alternative to do the proof of the conflict.[30] Indeed, in these countries, the access to the care is difficult because of the weak economic capacity of the population and the absence of the most stripped system of insurance. Moreover, the MRI is inalienable and inaccessible. In our low outcome country, we have two low-fields MRI for 6 million inhabitants. It means that efforts remain to be made.

The positive diagnosis of neurovascular conflicts is based on major criteria (neurovascular contact on the level of the REZ, the way how the nerve is deviated in the cistern) and on a minor criterion (remote contact of the REZ). The imagery 3DT2 with high resolution in combination with the angio-MR-3DTOF is a reliable technique to detect the conflict and to predict the grade of compression.[28,31] Figure 3 shows a crossing with right angle between the right AICA and the ipsilateral facial nerve translating a HFS. Figure 4 shows a crossing enters V and the basilar artery with cisternal way deviation of the nerve.

The classification of Sindou et al (made on a series of trigeminal neuralgia) distinguishes three grades of neurovascular conflicts.[32] Grade I corresponds to a simple contact on the

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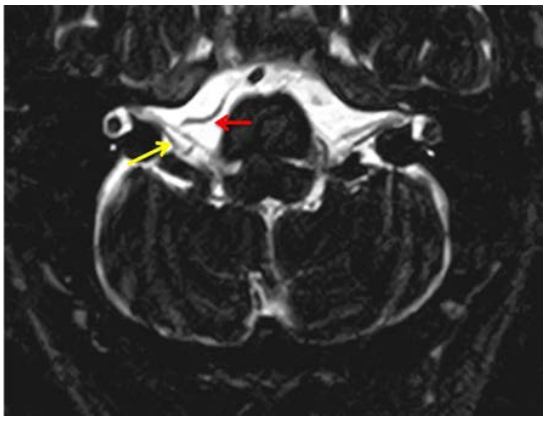

Figure 3: Axial sequences 3DT2 showing a crossing with right angle between the right AICA (red arrow) and the facial nerve ipsilateral (yellow arrow) translating a neurovascular conflict.

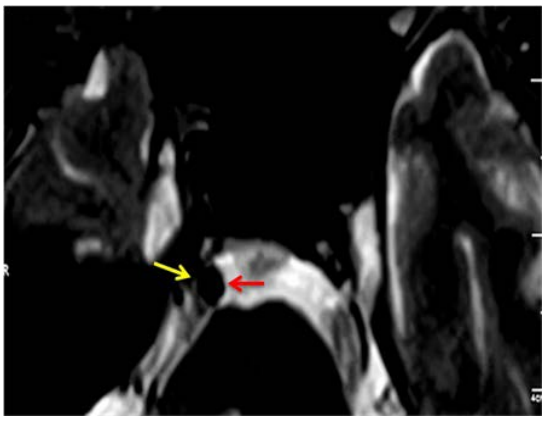

Figure 4: MRI aspect showing a crossing enters V and the basilar artery (red arrow) with cisternal way deviation of the nerve (yellow arrow).

nerve, whereas grade II corresponds to a contact with nerve distortion or displacement. Grade III is associated with indentation on the nerve.

The classification of Adamczyk et al[33] shows the evaluation criteria and the relation between arteries and trigeminal nerve. They distinguish 5 grades:

0: Absence of neurovascular contact;

1: Artery and nerve come into contact and their axes are parallel;

2: Artery and nerve come into contact and they cross each other by a straight or acute angle;

3: Contacting artery dislocates the nerve;

4: Artery and nerve come into contact, nerve atrophy is visible.

The degree of anatomical relationship between vessel and the cranial nerve VII was graded by Lagalla et al[17] as follows: 0=adjacent; 1=closeness; 2=contact; 3=distortion; 4=indentation.

DIFFERENTIAL DIAGNOSIS

The same symptoms of HFS, TN and GN are common to many disorders such as tumors, arachnoid cysts, epidermoid cysts, neuroglial cysts, facial myokymia, blepharospasm and facial tic.[34-42] Generally, this is not an issue since differential diagnosis is possible by studying the MRI findings and the clinical manifestation of the disease.

TREATMENT OF TN, HFS AND GN

The treatment of neurovascular conflicts of CPA is conservative or interventional. The medication of choice is carbamazepine in trigeminal/glossopharygeal neuralgia whereas botulinium toxin injection is used in the treatment of hemifacial spasm.

Microvascular decompression is an important procedure for the management of microvascular compression syndromes in the CPA like TN or HFS. The ability to identify the offending vessel is the key to success.[19,32] The endoscope helps surgeons to identify and understand the responsible conflict in order to treat them. Endoscopy improves visualization of the cranial nerves and allows seeing and understanding the neurovascular conflicts, which are not able to be observed using the microscope alone for certain patients.[43] The endoscope is a useful adjunct to microscopic exploration of the cranial nerves in the CPA avoiding significant cerebellar or brainstem retraction. The most important thing for a successful microvascular decompression operation is to remove the offending artery off the nerve. However, if the conflict site failed to be approached after endeavors, a successful microvascular decompression can still be achieved by relocating the offending artery with the guidance of real-time electromyography even without visualization of the confliction.[44]

The efficacy of endovascular treatment for neurovascular conflicts in the CPA caused by intracranial aneurysms and intracranial arteriovenous malformations, including TN, HFS, and GN, have been investigated.[45] The authors have concluded that endovascular treatment is a feasible and less invasive approach for relief of neurovascular conflicts in the CPA caused by intracranial aneurysms or intracranial arteriovenous malformations and could be considered as a therapeutic option in these situations.[45]

Other techniques for the treatment of TN and GN that were reported in the literature include:

- Treatment achieved with thermocoagulation or in exceptional cases by anesthetic block for diagnostic purposes[46];
- The optimal radiation dose and target of Gamma-knife radiosurgery for medically refractory idiopathic trigeminal neuralgia[47];
- Use of Gamma Knife radiosurgery for recurrent glossopha-

ryngeal neuralgia after microvascular decompression[48];

- Use of endotracheal tube surface electrodes to help delineate the sensory and motor vagal rootlets which may be sacrificed during the surgical treatment of glossopharyngeal neuralgia[49];
- Use of electrophysiological monitoring on selective rhizotomy of the glossopharyngeal nerve.[50] Electrophysiological monitoring in selective rhizotomy treating glossopharyngeal neuralgia can improve the efficiency of pain relief and reduce the incidence of complications.

MRI permits to identify the segment of the nerve which is atrophied. Indeed, TN is associated with atrophy of the REZ of the affected nerve compared with the asymptomatic side, but volume loss in different segments of the nerve has very different prognostic implications. Proximal atrophy is associated with vascular compression and correlates with improved outcome following microvascular decompression. However, distal atrophy is associated with a significantly worse outcome after microvascular decompression.[51]

CONCLUSION

The clinical manifestations of the neurovascular conflict of the CPA vary according to the affected nerve. High-field MRI remains the gold standard method in their diagnosis; but alternatively, the low-field MRI might be similarly useful. Treatment of TN, HFS and GN is initially by medicine but the intractable conditions may need interventional acts which constitute the only curative treatment.

AUTHORS CONTRIBUTIONS

All authors have contributed to the conception and design of the manuscript. They have been involved in drafting and revising the manuscript. All authors read and approved the final manuscript.

COMPETING INTEREST

The authors declare that they have no competing interests.

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