Clinical Study of Non-Migraine Primary Headache and Secondary Headache Associated to Different Pathological Conditions

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Received date: August 20, 2021; Accepted date: September 2, 2021; Published Date: September 10, 2021


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ABSTRACT

We have clinically examined 29 patients with non-migraine headache types (100%), eleven patients with headache and high blood hypertension associated with different pathologies (37%), ten patients with tension headache (34%), five cases with posttraumatic headache (17%), four cases with headache and microangiopathy and leukoencephalopathy (13%), three cases of tension headache (10%), three cases with headache and neurobehavioral disorders (anxiety and depression, mood changes, aggression) (10%), two cases with headache and facial paralysis (6.8%), one case headache with Alzheimer disease and senile dementia (3%), one case with headache and Parkinson diseases (3%), and one case with anaemia (3%) and metabolic disorders. The clinical findings are discussed in relationship with Retino-Hypothalamic-Pineal (RHP) axis, disturbances in normal sensory processing, sleep disorders, trigeminal neuralgia, facial paralysis, neurobehavioral and disorders. We have emphasized the differential diagnosis with migraine subtypes.

Keywords:
Headaches, Tension headache, Post-Traumatic headaches, Microangiopathy, Leukoencephalopathy, Vascular dementia, Cardiovascular diseases, High blood pressure, Neurologic diseases

Introduction

Understanding of pathophysiology of Tension-Type Headache (TTH) is paramount for the development of effective treatments and prevention of chronification of TTH [1]. The three subtypes of TTH are infrequent episodic, frequent episodic, and chronic tension-type headache [2]. Sleep disorders has been reported in tension-type headache [3,4]. Comorbid anxiety and depression among individuals with TTH has also been observed [5].

Chronic Daily Headache (CDH) represents a group of any headache disorder that occurs on a daily or near-daily basis, for longer than 6 months. Even though it is a common problem, it is not a well-defined disorder, resulting in controversies regarding its identification, description, and approach [6]. Chronic Daily Headache (CDH) represents one of the most challenging medical conditions that a health care provider is called on to treat. Four specific subtypes of CDH are covered: chronic tension-type headache, new daily persistent headache, and hemicrania continua [7].

There have been descriptions of aura occurring in association with cluster headache, hemicrania continua, and even with chronic paroxysmal hemicrania. In addition, the occurrence of aura without headache or followed by a headache resembling the criteria of tension-type headache is encountered in clinical practice [8].

Headache of the thunderclap variety become severe in intensity within seconds to a minute of onset. Although subarachnoid hemorrhage is usually the initial consideration, a multitude of other etiologies has been identified. The reversible cerebral vasoconstriction syndromes, terminology recently introduced to unify several disorders all presenting with thunderclap headache and similar diagnostic findings including reversible vasoconstriction of the intracranial arteries [9]. The headache due to subarachnoid aneurysmal hemorrhage presents peculiar characteristics (thunderclap, acute presentation, and high intensity), whereas in cerebral vasoconstriction syndrome, the short duration and the relapsing-remitting course of the thunderclap headache are key points for the diagnosis. In cervico cerebral artery, dissection pain is most commonly ipsilateral to the dissected vessel and is mainly perceived in the temporal area in case of carotid artery dissection and in the occipital area in case of vertebral artery dissection. In cerebral venous thrombosis, pain is often acute or subacute and severe; unfortunately, it may resemble a typical migraine attack or a tension-type episode; by the contrary, in primary angitis of the central nervous system, pain is always subacute or chronic with mild-to-moderate intensity; finally, in brain arteriovenous shunts such as malformation or fistula, pain is more frequently a clue for disease complication such as hemorrhage from the malformation or thrombosis of the draining vein [10].

The Trigeminal Autonomic Cephalagias (TACs) include cluster headache, paroxysmal hemicrania, and short-lasting neuralgiform headache attacks with conjunctival injection, tearing, and hemicrania continua [11].

The interaction between sleep and primary headache has gained considerable interest due to their strong, bidirectional, clinical relationship. Several primary headache demonstrate either a circadian/circannual rhythmicity in attack onset or are directly associated with sleep. The hypothalamus has emerged as a key brain area in several headache disorders including...
migraine and cluster headache. It is involved in homeostatic regulation, including pain processing and sleep regulation, enabling appropriate physiological responses to diverse stimuli. It is also a key integrator of circadian entrainment to light, in part regulated by Pituitary Adenylyl Cyclase-Activating Peptide (PACAP). With its established role in experimental headache research, the peptide has been extensively studied with headache in both humans and animals; however, there are only a few studies investigating its effect on sleep in humans [12].

New Daily Persistent Headache (NDPH) presents with a sudden onset headache which continues without remission within 24 hs. The exact pathogenic mechanism of NDPH is unknown, however, pro-inflammatory cytokines and cervicogenic problems might play a role in its development [13].

Headache is a milestone in cerebrovascular disorders; indeed, it may represent the only symptom at onset or predominates over the other neurological features. Unfortunately, headache associated with cerebrovascular diseases lacks clear-cut characteristics as it may resemble a migraine attack, tension-type headache, or cluster headache [14].

In the present study, we have examined from the clinical point of view 29 patients with the following headache subtypes: Headache associated to blood hypertension, posttraumatic headache and headache associated to neurobehavioral disorders (anxiety, depression and senile dementia), cephalic post coito and headache associated to blood hypertension, neurological disorders, such as facial paralysis, Parkinson and Alzheimer diseases, trigeminal neuralgia, and in metabolic diseases such as diabetes and hypothyroidism.

**Material and Methods**

**Case reports**

**Case 1:** LL, 18 years old, F. Left post-traumatic temporal headache after fall from a tree.
Diagnosis: Posttraumatic headache

**Case 2:** AS, 45 years old, F. Fall from a horse. Pain in the neck irradiated to the head. Blood hypertension, diminished vision acuity. 
Diagnosis: Posttraumatic headache, blood hypertension

**Case 3:** EM, 81 years old, M. Patient fall. Frontal posttraumatic headache. Left hemiparesis after 10 days. Blood hypertension. Axial tomography showed ventriculomegaly and prominent dilation of back ventricular horns.
Diagnosis: Posttraumatic headache, blood hypertension

**Case 4:** DC. 62 years-old. M. Brain trauma in the occipital region after motor vehicle accident, diplopia, clouded vision, high blood pressure, gastric ulcer and constipation.
Diagnosis: Posttraumatic headache, high blood pressure, diplopia.

**Case 5:** NJ, 59 years old, M. Occipital headache. Severe brain trauma at occipital region after fall. NMR image showed ischemic vascular lesions at frontal and temporal regions.
Diagnosis: Posttraumatic headache, ischemic vascular lesions and demyelinating disease.

**Case 6:** DC, 61 years old, M. Holocranial headache, blood hypertension, anxiety, hyperphagia.
Diagnosis: Headache, blood hypertension, anxiety.

**Case 7:** AA, 66 years old, M. Cephalea post coito, dizziness, high blood pressure, cold sweat, and sleep disorders.
Diagnosis: Cephalea post coito and blood hypertension

**Case 8:** NQ, 64 years old, M. Tension headache, blood hypertension, left facial paralysis, edema of right eye, rhinitis and sinusitis. History of previous Zika syndrome. The patient is Art painter and heavily exposed to oleo and benzene vapors.
Diagnosis: Tension headache, blood hypertension, left facial paralysis and exposition to oleo and benzene vapors.

**Case 9:** FO, 45 years–old, F. Holocranial headache, iron deficiency, anaemia, sleep disorders, depression, stress, polycystic ovary, irritable bowel syndrome, and loss of weight.
Diagnosis: Tension headache, anaemia, polycystic ovary, depression irritable bowel syndrome.

**Case 10:** AM, 55 years old, F. Holocranial headache, stress, dizziness, sleep disorders, muscle, and joint pains.
Diagnosis: Tension headache, dizziness, sleep disorders

**Case 11:** KL, 40 years old. F. Holocranial headache after psychic stress, low blood pressure, astigmatism, Nephrectomy of one kidney after a car accident.
Diagnosis: Episodic tension headache

**Case 12:** WV, 22 years old, F. Daily occipital headache, sleep disorders, labor stress.
Diagnosis: Daily occipital headache, tension headache.

**Case 13:** EM, 85 years old, F. Holocranial headache, vertigo, clouded vision, memory disorders, high blood pressure, hearing noise, and conjugal stress.
Diagnosis: Tension headache, conjugal stress, high blood pressure and vertigo.

**Case 14:** LL, 29 years old, F. Holocranial tension headache, clouded vision, anxiety, and panic crisis.
Diagnosis: Chronic tension headache, anxiety, panic crisis.

**Case 15:** MS, 35 years old, F. Tension Headache. Labor stress, cold sweating, and dizziness.
Diagnosis: Chronic tension headache, dizziness, and cold sweating.

**Case 16:** DJ.17 years old, F. Tension headache. Relatives and labor stress, memory disorders.
Diagnosis: Tension headache. Stress.

**Case 17:** LO, 54 years old, F. Holocranial headache, blood hypertension, dizziness, labor stress, sleep disorders.
Diagnosis: Holocranial headache, blood hypertension, tension headache.

**Case 18:** NT, 23 years old, M. Frontal headache referred to neck and shoulders, mood changes, depression, self-aggression. Normal blood tension.
Diagnosis: Headache, depression, mood changes, aggression.

**Case 19:** LL, 29 years old, F. Holocranial headache, clouded vision, anxiety and panic crisis.
Diagnosis: Headache, anxiety, panic crisis.

**Case 20:** AB, 60 years old, F. Headache and left facial paralysis, the sensation of the numb tongue. Allergic to air pollutants, thyroid nodule, and hypothyroidism.
Diagnosis: Headache, Facial paralysis, Allergic to air pollutants, and hypothyroidism.

**Case 21:** JA, 76 years old, holocranial headache, right palpebral ptosis, diabetes, high blood pressure, Patient received aortocoronary bypass surgery.

Diagnosis: Headache, diabetes, high blood pressure, and aortocoronary bypass surgery.

**Case 22:** VG, 50 years old, F. Headache, head jerking, generalized body tremor, sleep disorders, gait disturbances, speech disorder, hypoxic-ischemic encephalopathy.

Diagnosis: Headache, Parkinson disease, hypoxic-ischemic encephalopathy, 

**Case 23:** MP, 53 years old, F. Headache, neck pain, head jerking, body tremor, and heavy feeling in the left leg. Family history of Parkinson's disease.

Diagnosis: Headache and Parkinson's disease.

**Case 24:** EM, 85 years old, F. Holocranial headache, vertigo, clouded vision, memory disorders, high blood pressure, hearing noise, and conjugal stress.

Diagnosis: Holocranial headache, high blood pressure, stress

**Case 25:** 80 years old. Holocranial headache, recent memory disorders, diminution of visual acuity, gait disturbances. NMR images showed arteriosclerotic leukoencephalopathy and microangiopathy, brain atrophic changes. Carotid Doppler showed thickening of miointimal carotid system.

Diagnosis: Holocranial headache, vascular pathology, leukoencephalopathy and microangiopathy

**Case 26:** FL, 73 years old, M. Matinal headache. Patient with mixed Alzheimer disease and senile dementia., high blood pressure, aggression, sleep disorders, and lack of sphincter control.

Diagnosis: Matinal headache, mixed Alzheimer disease, and senile dementia

**Case 27:** MP, 76 years old, F. Intense frontal headache and left the hemifacial region. Trigeminal neuralgia and high blood pressure. RMN image showed arteriosclerotic leukoencephalopathy and microangiopathy.

Diagnosis: Frontal headache, Trigeminal neuralgia, and high blood pressure, leukoencephalopathy, and microangiopathy.

**Case 28:** GB, 43 years old. Intense holocranial headache, convulsive syndrome, vertigo, and scintillants scotoma, NMR image showed pituitary cyst and subcortical leukoencephalopathy.

Diagnosis: Holocranial headache, convulsive syndrome, vertigo, pituitary cyst, and subcortical leukoencephalopathy

**Case 29:** IG, 88 years old, F. Intense headache, dizziness, paresis of both legs, gait disturbances, sleep disorders, diminution of visual acuity and memory disorders. NMR images showed arteriosclerotic leukoencephalopathy and microangiopathy.

Diagnosis: Headache, paresis of both legs, gait disturbances, arteriosclerotic leukoencephalopathy, and microangiopathy.

**Interpretation of results**
We have clinically examined 29 patients with non-migraine headache types, (100%), eleven patients with high blood hypertension associated to different pathologies (37%), ten patients with tension headache (34%), five cases with posttraumatic headache (17%), four cases with microangiopathy and leukoencephalopathy (13%), three cases of tension headache (10%), three cases with neurobehavioral disorders (anxiety and depression, mood changes, aggression) (10%), two cases with facial paralysis (6.8%), one case with Alzheimer and senile dementia (3%), one case Parkinson diseases (3%), and one case with anaemia (3.%). The clinical findings are discussed in relationship with Retino-Hypothalamic-Pineal (RHP) axis, disturbances in normal sensory processing, sleep disorders, trigeminal neuralgia, facial paralysis, neurobehavioral and metabolic disorders. We have emphasized the differential diagnosis with migraine subtypes.

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**Discussion**
We have found nine female patients with tension-type headache subtypes. Two of them with episodic type headache, three with chronic headache subtypes, and two with mixed tension headache type and two with labor stress. These patients exhibited some of the following symptoms: psychic, labor o conjugal stress, and the following comorbidities: sleep disorders, anxiety, depression, blood hypertension, and irritable bowel syndrome.

Fuensalida-Novelo et al., (2019) [15] observed gender differences in variables associated with headache burden in tension-type headache. Fibromyalgia and tensional headache are two of the most prevalent functional disorders. Both seem to imply relationships with processes of the psychopathological sphere [16]. The most recent theories on Tension-Type Headache (TTH) occurrences suggest that a myofascial component, Through Trigger Points (TP), gives rise to pain signals from the periphery to the Central Nervous System (CNS). These nociception could lead to CNS sensitization and headache [17]. On the contrary, Do et al. (2018) [18] consider that myofascial trigger points are accumulated over time as a consequence of tension-type headache rather than contributing to the pathophysiology. We have observed labor and home stress, anxiety, depression, and sleep disorders in most patients examined. Current research into the pathogenesis of Tension-Type Headache (TTH) and migraine is focused on altered nociceptive pain processing. Among the potential factors that influence sensitization mechanisms, emotional stress, depression, or sleep disorders all have an essential role, they increase the excitability of nociceptive firing and trigger hyperalgesic responses [19].

We have observed patients with symptoms resembling a migrainous spectrum, such as vertigo, dizziness, and red eyes. A controversy exists about whether tension-type headache and migraines represent a continuum of the same pathophysiological process [21]. Possible peripheral mechanisms leading to pericranial tenderness include activation or sensitization of nociceptive nerve endings by liberation of chemical mediators such as bradykinin, serotonin, substance P) [20].

The diagnosis of Tension-Type Headache (TTH) is divided into two categories: episodic TTH and chronic TTH. It is important to differentiate TTH from other headache, including primary and secondary headache. Significant overlap in the diagnostic
criterions makes it difficult to differentiate TTH from other headache disorders and, in particular, migraines. A controversy exists about whether TTH and migraine represent a continuum of the same pathophysiological process [21].

Pericranial myofascial mechanisms are probably of importance in episodic tension-type headache, whereas sensitization of central nociceptive pathways and inadequate endogenous antinociceptive circuitry seems to be more relevant in chronic tension-type headache [22]. Chronic tension-type headache has been confirmed by the findings of generalized pain hypersensitivity both in the skin and in muscles and of a decrease in the volume of gray matter in brain structures [23]. Sensitization of pain pathways in the central nervous system due to prolonged nociceptive stimuli from pericranial myofascial tissues seems to be responsible for the conversion of episodic to chronic TTH [24].

We observed three patients with tension-type headache and sleep disorders. Sleep dysregulation triggers episodic Tension-Type Headache (TTH), and sleep disorders may complicate and exacerbate a headache. Insomnia is a risk factor for new-onset TTH. Chronic Tension-Type Headache (CTTH) is the most common headache secondary to sleep apnea and other sleep-related breathing disorders [25].

Four patients exhibited neurobehavioral disorders, such as psychic stress, anxiety, depression and panic attack. Psychiatric disorders are comorbid with both TTH and insomnia [26]. As in migraine, in TTH too, evidence has been found of comorbidity between headache and psychiatric disorders, including depression and anxiety disorders. Psychological factors and emotional disturbances have been indicated as risk factors for TTH [27].

In addition, we have found a case with irritable bowel syndrome. Tajti et al. (2017) [28] reported that tension-type headache is common among patients with ulcerative colitis. According to these Authors, this observation raises the question of whether stress plays role in the pathogenesis of both diseases. According to Lighthart et al. (2018) [29], migraine and Tension-Type Headache (TTH) are often viewed as distinct entities and defined as such in the International Classification of Headache Disorders, 2nd edition (ICHD-II) criteria. However, these Authors postulated that according to twin family data migraine and Tension-Type Headache (TTH) share genetic factors. This issue requires further clinical and basic research studies on genetic neuroscience.

Russell et al. (2007) [30] studied the importance of genetic and environmental factors in tension-type headache using a genetic modeling analysis and concluded that genetic effects contribute to nearly half of variance in the liability to tension-type headache.

We have found headache in the whole population studied. A putative role of the Retino-Hypothalamic-Pineal (RHP) axis in the pathophysiology of primary headache is reviewed by Deshmukh (2006) [31] in terms of (1) retinal dysfunction, (2) hypothalamic dysfunction and human circadian desynchrony, (3) pineal melatonin dysfunction and (4) rostral limbic dysfunction mediating the human stress response. The author postulates a Unified RHP hypothesis, suggesting that an acute, periodic or chronic, circadian desynchrony and dysfunction of the whole or part of the RHP axis is implicated in the pathophysiology of primary headache. From the anatomical perspective, there are close fiber connections between the hypothalamus and the trigeminal nucleus caudalis, thus reinforcing the importance of diurnal rhythm disturbance in the pathophysiology of headache disorders.

The hypothalamus forms part of the central autonomic network, regulating body homeostasis and controlling pain. To this effect, it is strongly wired to more rostral and caudal areas, in particular the brainstem periaqueductal grey, the locus coeruleus and the median raphe nuclei, all involved in autonomic and sleep mechanisms and also in the descending control of pain perception. The hypothalamus, especially its posterior regions, becomes activated during attacks of the Trigeminal Autonomic Cephalalgias (TACs), while brainstem, especially dorsal pontine, activity shows up during migraine attacks. The hypothalamus and interconnected brainstem areas likely represent the neural sites responsible for the chronobiological features of some headache, in particular the sleep-related attacks typical of the TACs, migraines and hypnic headache [32].

Cluster headache is clinically characterized by headache attacks that recur in chronologically similar patterns and the presence of the cluster period. A polymorphism of the orexin receptor 2 gene has been identified as a risk factor for developing cluster headache. Orexin may be a key molecule closely implicated in both biological rhythm and nociception. As with cluster headache, structural abnormalities of the hypothalamus have been detected by voxel-based morphometric assay [33]. While cluster headache has traditionally been thought of as a vascular headache disorder, its periodicity suggests the involvement of the suprachiasmatic nucleus of the hypothalamus, the biological clock. Normal circadian function and seasonal changes occurring in the suprachiasmatic nucleus and pineal gland are correlated to the clinical features and abnormalities of circadian rhythm seen in cluster headache [34].

In the present study, we have found posttraumatic headache in 27% of patients studied. According to Lucas et al. (2012), headache is one of the most common and persistent symptoms following Traumatic Brain Injury (TBI) [35].

We have reported sleep disorders in six patients. According to Caminero-Rodriguez and Pareja (2008) [36], the relationship between headache and sleep is complex and runs in two directions. Headache may be the consequence of a (primary or secondary) sleep disorder or its cause (in chronic tension-type headache and/or chronic migraine with or without painkiller abuse). It can also be related to sleep in an intrinsic way, as in the case of hypnic headache (which only appears during sleep) or other primary headache, such as migraine and certain trigeminal-autonomic cephalalgias (which can appear during the waking state or during sleep). This type of headache occurs mostly during REM sleep.

In disorders such as primary headache, dysfunctions affecting brain regulation mechanisms contribute to the generation of episodic painful states in susceptible individuals, and to the evolution from acute to chronic migraine or cluster headache. Taken together, these studies support the concept that CNS mechanisms that process trigemino-vascular pain do not consist only of a bottom-up process, whereby a painful focus
modifies the inputs to the next higher level. Indeed, several CNS regions mediate subtle forms of plasticity by adjusting neural maps downstream and, consequently, altering all the modulatory mechanisms as a result of sensory, autonomic, endocrine, cognitive and emotional influences. Disturbances in normal sensory processing within these loops could lead to maladaptive changes and impaired craniofacial functions at the origin of primary headache [37].

We have herein reported one case with trigeminal neuralgia. The trigeminal ganglion plays a key role in primary headache pathophysiology. Calcitonin gene-related peptide (CGRP) and CGRP receptors are expressed in trigeminal neurons that form C-fibers and A-fibers, respectively. In acute migraine and cluster headache attacks, there is the release of CGRP into the cranial venous outflow [38].

In the present study, we have reported a case of headache with hypothyroidism. Headache is one of the most common symptoms of hypothyroidism, occurring in approximately one-third of the patients. To date, data about the relationship between migraine and tension-type headache and thyroid dysfunction, and in particular hypothyroidism have been contradictory, while the underlying pathophysiological basis explaining this association is still unclear [39].

Most cases studied exhibited daily headache. The new daily persistent headache (NDPH) exact pathogenic mechanism of NDPH is unknown, however, pro-inflammatory cytokines and cervicogenic problems might play a role in its development [13]. We have herein reported neurosensory disorders, such as hearing noise, hypoacusia, visual disorders, diplopia, and scintillant scotoma. The risks of tinnitus, sensorineural hearing impairment and sudden deafness were found to be significantly higher in patients with non-migraine headache than in those without headache [40].

Current understanding of the origin of occipital headache falls short of distinguishing between cause and effect. Most preclinical studies involving trigeminovascular neurons sample neurons that are responsive to stimulation of dural areas in the anterior 2/3 of the cranium and the periorbital skin. Central neurons receiving nociceptive information from the posterior dura are located in the C2-C4 spinal cord and that their cutaneous and muscle receptive fields are found around the ears, occipital skin and neck muscles. Occipital headache are common in both migraine and non-migraine headache. The posterior dura overlying the cerebellum is innervated by cervicovascular neurons in C2 DRG whose axons reach the posterior dura through multiple intracranial and extracranial pathways, and sensitization of central cervicovascular neurons from the posterior dura can result in hyper-responsiveness to stimulation of neck muscles [41].

Headache has been studied in patients with severe or moderately severe Meniere’s disease (MD) or with Meniere’s syndrome (MS). The MD patients exhibited significantly more occipital and neck headache than vestibular neuronitis (VN). Nonmigraine primary headache include trigeminal autonomic cephalalgias, primarily cluster headache; facial pain, primarily trigeminal neuralgia; and miscellaneous headache syndromes, such as hemicrania continua and new daily persistent headache. Symptomatic headache are numerous and in most cases are not the consequence of serious diseases, however, a tumor or a different cerebral disease can be taken into account. Accurate anamnesis and accurate physical examination will help in diagnosing the etiology of headache [25].

Merikangas et al (1993) [42] earlier study the association between personality, symptoms and headache subtypes in a prospective longitudinal epidemiologic study of a cohort of 19- and 20-year-olds. Persons with migraines with aura exhibited greater impairment than any of the other headache subtypes or controls. Subjects with tension-type headache did not differ from controls on any of the personality or symptom factors.

Conclusion

We have clinically examined 29 patients with non-migraine headache types (100%), eleven patients with high blood hypertension associated to different pathologies (37%), ten patients with tension headache (34%), five cases with posttraumatic headache (17%), four cases with microangiopathy and leukoencephalopathy (13%), three cases of tension headache (10%), three cases with neurobehavioral disorders (anxiety and depression, mood changes, aggression) (10%), two cases with facial paralysis (6.8%), one case with Alzheimer and senile dementia (3%), one case Parkinson diseases (3%), and one case with anaemia (3.%) and metabolic disorders. The clinical findings are discussed in relationship with Retin-Hypothalamic-Pineal (RHP) axis, disturbances in normal sensory processing, sleep disorders, trigeminal neuralgia, facial paralysis, neurobehavioral and disorders. We have emphasized the differential diagnosis with migraine subtypes.

Acknowledgment

This paper has been carried out with the administrative and logistic support of the Biological Research Institute. Faculty of Medicine. Zulia University, The San Rafael Clinical Home and the Castejón Foundation Maracaibo, Venezuela

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