MIGRAINE – A LOT MORE THAN A HEADACHE

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Migraine occurs worldwide and has been known since antiquity. Migraine is commonly defined as a chronic neurological disease characterized by recurring headache, usually affecting only one side of the head, characterized by sharp pain and often accompanied by nausea, vomiting, and visual disturbances.

Vasodilation of cerebral blood vessels has been considered to be of importance as a cause of migraine-related headaches. Vasodilator mechanism and neuropeptides therefore became the focus in research on migraine which gave rise to the concept of vascular headache. However, advanced studies of various vasodilators and functional brain imaging has made it clear that vascular changes are not the primary cause of migraine. The current consensus is that migraine is a neurovascular disease caused by a primary brain dysfunction which leads to activation and sensitization of the trigeminal system.[1]

In this review we would like to stress that there are many manifestations of migraine without headache, and migraine sufferers do not necessarily need to have classical migraine headache ever in their lives. Furthermore we want to conceptualize migraine as a genetically determined disorder of sensitization and discuss how different factors can trigger migraine manifestations of varying kinds.

Genetics

In recent years, breakthroughs have been made in understanding the genetic background of common migraine. Common migraine has proved polygenetic with several genetic loci and with a total heredity of almost 50%. [2] [3] [4] [5]

Common migraine is characterized by a high prevalence (10 - 20%) and a marked genetic heterogeneity. This means that different individuals may have different propensity to develop symptoms. (Some will get it very easily – other more seldom and maybe only after massive exposure to strong triggers)[6] [7]
The genetic changes in migraine affects ion channel function, exocytosis and synaptic reabsorption of neurotransmitters including glutamate - changes that affect neuronal excitability and facilitates synaptic transmission (transmission of nerve signals from nerve to nerve).[8] The genetic factors also interact with hormonal factors (e.g. contraceptive, estrogenic substances in food) and environmental factors (e.g. flickering light, fluctuating noise, pungent odors etc.) which can further trigger the neuronal excitability.[9] [10]

Pathogenesis

Migraine is characterized by increased neuronal depolarization with accompanying increased neuronal excitability and a higher propensity for synaptic transmission of nerve signals from nerve to nerve. Lower degree of sensory stimuli is required to activate peripheral sensory cells, lower degree of stimulation is required for depolarization of individual neurons and increased neuronal input reaches the brain stem. [11] [12]
The increased activation of the various centres in the brainstem includes increased activation of brainstem centres that regulate nociception and vascular control [13] . Increasing activity in these centres leads to increased stimulation of the whole central nervous system - increased cortical stimulation and increased stimulation of the midbrain.[14] Increased stimulation of formation reticularis often leads to an increased level of waking and sleep problems.

If stimulation exceeds a threshold, a cortical depolarization wave (cortical spreading depression) is triggered that slowly spreads from the occipital cortex and beyond. This wave of depolarization induces a contraction of the cortical blood vessels in the area, with accompanying local hypoperfusion (decreased blood flow) [15] [16] [17]
This blood vessel contraction with reduced blood flow is contra regulated by release of CGRP (and other vasodilatator neuropeptides) from trigeminal nerve-endings in the perivascular space - the so-called trigemino-vascular reflex.[18] [19] [20] The result is a pronounced vasodilation in the area with accompanying perivascular serous exudation, which secondarily leads to a more or less chronic sterile perivascular inflammation.[21] [22] Perivascular inflammation affects the surrounding cortical neurons and glia cells with accompanying cortical sensitization.[23] [24] Aura occurs in the phase of cortical spreading depression and headache occurs in the phase of vasodilatation.

The pathophysiology thus involves inherited alteration of cortical excitability, intracranial arterial dilatation, neurogenic inflammation, recurrent activation and sensitization of trigemino-vascular pathways, and consequential structural and functional changes. [25] [26] [22]

Sensitization in migraine

Sensitization means that a person becomes increasingly sensitive to stimuli. The reaction to a stimulus increases each time the stimulus is presented.
Peripheral sensory sensitization in migraine means that the threshold for nociceptive stimulation is lowered by easier activation of ion channels or lowered threshold for action potential in nerve cells. In migraine the genetic changes affects ion channel function, exocytosis and synaptic reabsorption of neurotransmitters including glutamate - changes that affect neuronal excitability and facilitates synaptic transmission (transmission of nerve signals from nerve to nerve).[8] That means that receptorcells will react more readily for less stimulation.

Central sensory sensitization in migraine is explained by the neuro-inflammatory long-term potentiation of glutamate synapses in the central nervous system induced by peripheral trigger. This long term potentiation may in time lead to debilitating chronic sensory hypersensitivity because of pathologically increased sensory sensitivity.

All types of strong persistent or fluctuating sensory input or a surfeit of trigger that activates nerve transmission (or combination of both) over time will accelerate the process of sensitization. [27] Repetitive stimulation of trigemino-vascular neurons creates a hyperexcitability in nearby neurons and induces central trigeminal and spinal sensitization causing neurons in the trigeminal nucleus caudalis to be activated by already minimal stimuli from peripheral receptors.[28] Increased serotonin secretion mediated via raphe nuclei in the brainstem and increased release of glutamate in synapses centrally together with the perivascular inflammatory stimulus results in an increased capacity to transmit pain impulses to the centers involved in the experience of pain (e.g. thalamus) and creates an increased central sensitization of varying degree that might end up in a vicious circle to a chronic state of extreme sensory hyper reactivity – chronic migraine. [29] [30] [31] [26] [28] [32]

Sensory hyper reactivity and the central sensitization means that even very weak pain signals are perceived as painfully sharp. A weak pain signal caused by vasodilatation of vessels in the brain will evoke migraine headaches, a light scratch on the skin will evoke painful allodynia and weak pain signals from achy muscles, ligaments and tendons might evoke chronic debilitating pain as fibromyalgia. [33] [34] [35] [36]

The sensory hypersensitivity can affect any sensory qualities more or less and may vary over time depending on the degree of sensitization.
Sensory hypersensitivity to one or more sensory stimuli (light, sound, infrasound, smell, vestibular motion stimuli, muscle sensory stimuli, tactile stimuli, painful stimuli, cold and heat stimuli, autonomic stimuli from internal organs) strongly suggests that the person has a genetic predisposition for migraine.[31] [30]

Fig. 1

Increased sensitivity to light (Photophobia)
Increased sensitivity to sound (Hyperacusis)
Increased sensitivty to smell (Hyperosmia)
Increased vestibulär sensitivity (Sea-sickness)
Increased proprioceptiv sensitivity (postural phobic vertigo)
Increased sensitivity to pain (cutaneous allodyni, fibromyalgia)
Increased sensitivity to touch and pressure
Increased sensitivty to cold and heat
Increased sensitivity of the autonomic nervous system (intestinal hyperreactivity with IBS like dyspepsia, nasal/laryngeal/bronchial hyperreactivity

Symptoms of central sensitisation.

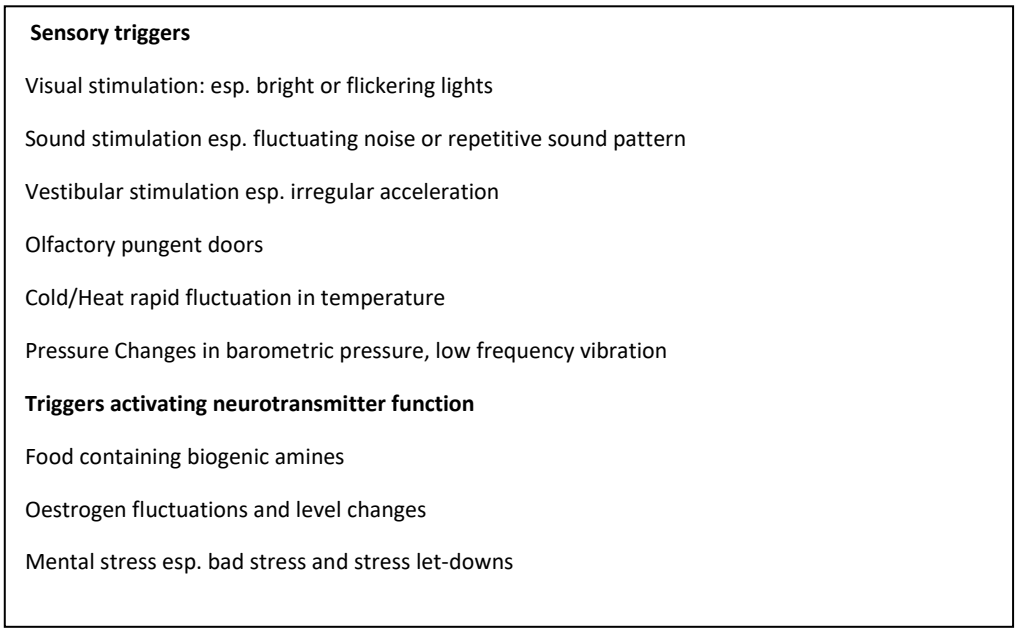
A person with migraine has a more sensitive nervous system that more easily reacts on external stimuli. This hypersensitivity can vary over time depending on hormonal changes, exposure for triggers (stress included) and degree of central sensitisation. The symptoms of hypersensitivity can vary from person to person and vary from one time to another. The most obvious symptoms of increased neuronal excitability in migraine is hypersensitivity to light and sound. However, in a person with migraine every single sensory system in the body can be hypersensitive (more or less pronounced) due to central sensitisation. The symptom of this hypersensitivity is not always obvious connected to headache and thus are often misinterpreted or not understood. Hypersensitivity of the vestibular system can be expressed as nausea, extreme seasickness, mal de debarcement syndrome, torticollis or postural instability. [37] [38] [39] [40] Although hypersensitivity to light is the most common sign of visual hypersensitivity there can be other expressions such as Cloudy vision, Sensitivity to visual patterns, such as stripes or graphs distorted vision, illusions or visual hallucinations. [41] [42] As for the olfactory system hypersensitivity to smell is most commonly noticed and olfactory hallucinations more seldom.[43] [44] [45] Hyperacusis and a disabling sense of pressure in the ear is common expressions of increased neuronal sensitivity seen in migraine but other expression in the auditory system might be sound distortion, auditory hallucination and tinnitus.[46] [47]A disabling feeling of pressure in the ear is an often misinterpreted symptom of neuronal hyperexitability in migraine. [48] Increased sensitivity in nocioception can be expressed as increased sensitivity to pain stimuli (tender spots in the scalp, tender points for n. supra- and infra-temporale and n. occipitalis) or increased sensitive to touch or cold [49] [50] and increased proprioceptive sensitivity can be expressed as light-headedness or postural vertigo. [51] [52] Increased visceral sensitivity might evoke IBS like abdominal pain and bloating. [53]

Migraine triggers

"Triggers" are specific factors that may increase the risk of having a migraine attack.

Triggers activate those processes that cause migraine in people who are prone to the condition. A certain trigger will not induce a migraine in every person; and, in a single migraine sufferer, a trigger may not cause a migraine every time. All types of sensory input, especially irregular, fluctuating or subjective distracting have the ability to trigger migraines. All stimuli that activate our sense organs have the potential to initiate migraine symptoms. The second type of trigger are factors that activate the neural transmission as estrogen, mental stress and food containing biogenic amines. [54] [55] [10] [56] [43] [57] [58] [59] [60] [61]

Fig2.



Different kinds of headache in migraine

The classical form of migraine headaches is half-sided headache of throbbing character combined with nausea and signs of sensory hypersensitivity as light and sound sensitivity. However, migraine headaches might also have other sites as the forehead or temples or bilaterally in the neck.
Localization of the headache might depend on the affected vascular area. Impact on the vertebral or basilar artery might elicit pain in neck or back of the head [62] Impact on the posterior cerebral artery might elicit pain in or around the ear and a vascular contraction in the area of the anterior cerebral artery and the ophthalmic artery might elicit pain localized to the forehead, base of the nose or behind the eyes. [63] [64] This latter type of migraine-headache is often misinterpreted as sinusitis (a frontal or maxillary sinus infection), atypical facial pain or dental pain. [65] [66] [67] [68] [69]

Migraine without headache

Vestibular migraine.

The official definition of vestibular migraine is based on recurrent vestibular symptoms, a history of migraine and one feature or more of following: headache, photophobia or hyperacusis and visual aura.[70]

A common variant of vestibular migraine is a pure rotational vertigo that can be combined with a feeling of fullness in one ear and tinnitus in the same ear. This type of vestibular migraine is often very similar Mb.Meniere and often confused with this disease. Unlike Mb.Meniere significant progressive hearing loss is missing as well as vestibular impairment. Vestibular migraine may have a duration from seconds to

hours to days. If this type of vertigo is combined with brainstem symptoms the vestibular migraine is called a basilar migraine.[70 71 72 73 74 75]

However vestibular migraine can manifest itself in several ways as general imbalance, light-headedness or short dizzyspells without other symptoms. A proprioceptive sensitization with hypersensitivity to proprioceptive input to vestibular nuchlei causes a debilitating postural dizziness with pronounced feeling of instability. Vestibular migraine may also manifest as extreme motion sickness.[76]

Reason for vestibular migraine may be an abnormal hyperactivity in the brain stem affecting the interpretation of vestibular and proprioceptive input as well as influence of altered blood flow in the vestibular and cerebellar arteries. Because there is direct projection of the trigeminal nuclei to the vestibular nuclei, it is possible that sensitized trigeminal neurons might increase the sensitivity of the vestibular neurons. On the other hand, there is evidence that vestibular input can be a powerful trigger for central sensitization.[77]

Fig.3

Strong rotatory vertigo with brainstem-symptoms (Basilar migraine)
Meniere-like attacks of rotatory vertigo with pressure sensation in one ear, tinnitus in one ear and nausea duration 1 – 2 days.
Short episodes of vertigo or dizziness without other symptoms
Paroxysmal vertigo with nystagmus in childhood
Spells of vertigo in seconds
Periods of unsteadiness
Phobic postural vertigo

Visual migraine

Visual migraine without headache is very common and often the visual phenomena are related to the "cortical spreading depression" as transient effects of electrical brain impulses starting in the occipital visual cortex. Positive visual phenomena often takes the form of an arcuate visual field loss with shimmering or glistening zigzag edges. Often there are flashes of light or color changes, less often visual hallucinations (Alice in Wonderland phenomenon). Visual migraines can also manifest as "visual snow" or negative scotoma with a blurred area of the visual field.

Visual migraine as effect of vasoconstriction may be expressed as temporary loss of vision or partial vision loss, double vision, blind spots, tunnel vision or loss of peripheral vision.[78 79 80 81 82 78 79 80 81 82]

Abdominal migraine

The diagnosis abdominal migraine is controversial. However some evidence suggests that recurrent episodes of distressing abdominal pain and bloated stomach in the absence of headache may be a type of migraine. Abdominal migraine causes pain in the abdomen that can be severe and debilitating. It is typically located in the middle portion of the belly, often around the umbilicus. Cramping, nausea, and vomiting can accompany the pain. Paleness of the skin is often observed. There may be no associated headache. The symptoms are usually relieved by sleep and can last anywhere from one hour to several days. Abdominal migraine seems most likely to affect children and mimic an appedicitis and the pain can last from hours up to several days.[83] Infantile colic and episodic vomiting in children are other manifestations of abdominal migraine.[84]

In adult female IBS-like abdominal bloating and abdominal pain is very common. The frequency of severe IBS in migraine patients is 25 - 50%. The migraine patients with long headache history, high headache frequency, and anxiety are more prone to be affected with IBS. The comorbidity of migraine and IBS may be attributed to the brain-gut axis and central sensitization.[85]

Audiologic migraine

Sudden hearing loss is common, but unexplained in many cases. Although usually attributed to a viral infection of the inner ear in most patients, the abrupt onset of the hearing loss in many patients argues against a viral etiology. There is strong evidence that migraine may elicit sudden deafness, fluctuating hearing (oscillocusis), tinnitus and dysacusis. [86 87 88 89]

Cognitive impairment, Fatigue, Confusional migraine and Transient global amnesia

Migraine with central sensitisation is frequently associated with cognitive and mental symptoms even without headache. Patients often find these symptoms to be some of the most significant contributors to their disability. Patients report experiencing issues with concentration, attention, planning, judgment, initiative, processing speed, memory and fatigue. This cognitive decline is connected with migraine activity and is not permanent. Most common is a transient cognitive decline in migraine without aura. Before, during and even after a migraine attack migraine sufferers report an overall lack of energy; fatigue is a hallmark symptom of migraine with central

sensitisation. In some, the tired feeling is a disabling migraine fatigue that interferes with daily activities and reduces the overall quality of life. By one estimate 67% of people with Chronic Migraine meet the criteria for a diagnosis of Chronic Fatigue Syndrome. [90] There is often a double burden as people with migraine often has sleepdisturbances - difficulty getting to sleep and maintaining sleep with frequent awakening.

More rarely occurs confusional migraine with disorientation, impaired memory, impaired speech, disorientation or even transient global amnesia with complete memory loss without headache. [91] [92] [93] [94] [95] A confusional migraine is a type of migraine that primarily affects children and teenagers. The main symptom is headache and a sudden state of intense confusion that occurs suddenly and lasts longer than the headache. The episode can be as short as 30 minutes or as long as 24 hours with symptoms that include: memory loss, anxiety, agitation, blurred vision, dizziness, speech impairment, disorientation, or a loss of a sense of place and time. Episodes are often followed by a period of deep sleep and recovery. Afterward, you may not remember what occurred, although you are alert as it is happening. The symptoms fade after the episode.

Alice in Wonderland syndrome is a state of confusion without headache that affects the perception. Patients experience visual, auditory and tactile hallucinations and altered perceptions. The most common symptom is an altered body image. The person experiences an incorrect size of different parts of the body. Another common phenomenon is a distorted sense of time: time seems to pass too quickly or pass at a snail's pace. Some people with Alice in Wonderland syndrome experience powerful visual hallucinations; they can visualize things that are not there. [96] [97] [98] [99] [100]

Transient global amnesia is characterized by a sudden onset of severe anterograde amnesia and confusion that often includes repetitive questioning. Patients are often disoriented in regard to time and place but usually not personal identity. There is no concomitant headache. Transient global amnesia typically lasts for hours, although its duration may range from minutes to days. Retrograde amnesia is also common, although its severity varies much more than that of anterograde amnesia. Retrograde amnesia is usually extensive and is temporally graded. As the anterograde amnesia gradually resolves, the temporal extent of the retrograde amnesia appears to shrink. After recovery, the patient retains an amnesia for the period of the transient global amnesia and often for a few hours preceding it.

Discussion

There is a general misconception that migraine is nothing but headache. In fact, a person with migraines may suffer from a completely different spectrum of strange and debilitating symptoms (with or without headache) that neither the patient nor

physician spontaneously associates with migraine. For these people it is easy to be regarded as a person with mental disorders or aggravating their symptoms.

Fig.4 Different symptoms that might occur in Migraine

All kinds of increased sensory sensitivity (Photophobia, hyperacusis, hyperosmia, etc..)
Different kind of headache (half-side, bilateral, frontal, occipital, “sinugenic” facial pain, pain behind eye, unilateral ear-ache)
Transient fullness or pressure in one ear
Abnormal perception of sound (hyperacusis, distortion, auditive hallucinations)
Sudden deafness
Tinnitus
Abdominal IBS-like pain, abdominal bloating
Vertigo, dizziness, feeling of postural instability , nausea, seasickness
Different visual sensations, visual hallucination, transient loss of vision
Transient global amnesia
Sleep disturbances
Fluctuating cognitive impairment
Depression, anxiety, irritability
Transient arm or leg weakness
Transint feeling pins and needles or numbness
And more….

Different parts of the brain as well as various specific sensory organs can be affected by various factors in the cascade of events involved in migraine progression. Symptoms may be triggered by aura (related to cortical spreading depression),

symptoms may be related to central sensitizing or an effect of hypoxia after vascular contraction. Although headache is the most alarming and clear manifestation of migraine, it is important not to lose sight of the whole complex of symptoms that can affect the person who has the genetic predisposition to migraine. Dizziness without the headache is an example of the most common manifestations of migraine without headache. But how many know that unpleasant feeling of pressure in the ear and ear ache can be a migraine manifestation - how many know that the recurrent "sinusitis" in young women is often a migraine manifestation? [65] [68]

Increased sensitization means that people with migraine who are constantly exposed to the trigger factors may develop ever more heightened and distressing sensitivity to sensory stimuli such as sound,, light and odor hypersensitivity or extreme motion sickness susceptibility.[101]

In migraine, sensory cells and nerves react more easily. The nervous system in subjects with a genetic disposition for migraine is unusually alert. Possibly as a consequence of that people with migraine (e.g. the genetic code for migraine) often have certain personal characteristics that might be a result of a different kind of activation in the central nervous system.
Increased activity in the brain stem reticular formation will result in an increased level of alertness: People with migraine often experience a disturbed sleep pattern - often sleep deprivation disorders type: sleep disruption, easily aroused, wakes up frequently at night. Increased activity in the serotonin system involves a tendency for increased anxiety and depression. People with migraine are more often prone to depression and anxiety disorders. Impact on centers for vascular control would give a tendency to vasoconstriction and a slightly impaired peripheral circulation with increased sensitivity to cold as a result and an increased tendency to develop Raynaud's phenomenon. Such an effect on circulation also means an increased risk of heart attack and stroke.[102] [103] [104] [105]

But the increased neuronal excitability not only has a negative impact. Such a general and widespread genetic change would hardly be left over for generations if there were not also some positive qualities for the individual.

The change in neuronal properties that the genetic changes bring with them will likely give rise to characteristic positive personality characteristics. A general impression of people with migraine is that they are often ambitious, dutiful, proper - orderly - pedantic, determined – driven. They seem to associate more easily and also have improved sensory and memory qualities etc. - qualities that all together allow people with these genetic changes to compete better. [106] [107] [108]

But they also might be more sensitive to modern society's influences in the form of increased load of sensory triggers (light - sound - smell and touch stimuli, low frequency vibration from air condition fan and wind turbines), hormonal (birth control pills, estrogen replacement, traces of hormones in food and drinking water,

estrogen-like substances in diet) and increasing amounts of biogenic amines in the diet (increased use of convenience foods with additives as glutamate). Perhaps this might partially explain the increasing tendency to poorly understood syndromes, depression and burnout in today's society, especially among women. [109] [110]

So maybe we should not see migraine as a headache-disease, but as a genetic variation of Homo sapiens with an increased neurogenic sensitivity, for good or for bad.

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