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SPECIAL ARTICLE

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Mathematic models of migraine

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Abstract This article describes the mathematical process of building a model of migraine syndrome guided by research data and evidences. The paper illustrates the construction of a new possible model of the evolution, in the time, of migraine. The model is an artificial network using cost-effective, conventional pure and mixed mathematical methods. It can enable to reconstruct the rules needed to give homogeneity to an incomplete data set on which we require a correct prediction and reproduction. Such a methodology represents an attempt to offer a complete output model consisting of a virtual, complex structure capable of simultaneously taking into account sparse and apparently incongruent evidences of a complex disease such as migraine. This is a model that addresses the complex rules aand relationships among inherited hyperalgesia, migraine stemming off and its further worsening. Such a construction is needed as a platform for any further artificial, non-linear neural network.

Key words Migraine • Experimental model • Maths • Wohler curve • Genetic abnormality • Crack propagation

The nature of migraine

The skilful observation of the clue symptoms and biochemical data of a disease may enable researchers to identify the nature and the mechanism of the disease under observation. The pivotal characteristics of migraine are evident during a great attack which consists of pain and "vegetative symptoms" consisting of:

Σ Sensory system activation = pain + metesthesias (i.e. non painful, unpleasant visceral sensations) and vegetative system activation symptoms = migraine attack

To propose an up-dated, adequate animal model of migraine seems incorrect since we are today unable to reproduce the simultaneous stemming off of the previously mentioned categories of symptoms in the animal.

The pavement for the evolution of the studies on migraine is represented by the 5-HT theory produced by Federigo Sicuteri in the period 1960-1973 [1–4]. The theory, based on clinical pharmacology data highlighting the action of 5-HT agonist and antagonist in migraine attack and prophylaxis, gave rise to other pharmacological and clinical pharmacological outcomes [5]. That does not mean we are in front of a mere "serotonergic disease". As a matter of fact, this statement was clear-cut since the observation that parachlorophenylalanine, a depletor of neuronal 5-HT, was able to induce severe pain in subjects with a personal history of migraine, while the drug was devoid of any effect when given to subjects absolutely exempt from migraine [3, 6]. The outcome underlines that migraine needs a ground abnormally sensitive to monoamine turnover. Moreover, our group recently demonstrated in rodents that serotonergic drugs such as sumatriptan induce analgesia by means of cholinergic central system activity [7, 8]. That seemingly means that several neurotransmitters are involved in the stemming off of a migraine attack. Thus, it seems incorrect to propose a "one-transmitter" biochemical model for studying migraine. Similarly, it seems incorrect to propose any animal model based either on changes of one-receptor type or on pain-related behaviour since these phenomena can

represent only a fragment of the entire problem. The introduction of a mathematic model can be either the correct reference for testing the interest and validity of animal models and genetic studies or the correct way to coagulate sparse biochemical and clinical pharmacology data.

To clearly state the nature of migraine we have to criticize the following formula:

A Pain (sensory system activation) + B Σ Metesthesias (sensory system activation) and vegetative symptoms (vegetative system activation) = AB - migraine attack

Here, A is pain not due to an adequate stimulation of nociceptor/polymodal receptor and B consists both of vegetative symptoms and metesthesias (i.e. nausea, vomiting, weakness and fatigue sensation, breathlessness sensation).

The first observation is that A and B do not represent addenda. Indeed, they are parallel phenomena. Moreover, metesthesias and vegetative symptoms cannot be considered at the rate of a reaction as it can happen in physiological pain where Pain → Reaction. This means that migraine attack is different from any other pain since vegetative symptoms and metesthesias are phenomena parallel to pain. Indeed, vegetative phenomena only apparently look like a Reaction. Thus, we can summarize as follows: Pain--- "Metesthesias and vegetative phenomena = Migraine. Indeed, migraine cannot be included in the Pain → Reaction Group of "Group Theory Math" since it conversely consists of parallel phenomena, i.e. Pain--- "Reaction-like Phenomena". This means that migraine is an absolutely new pain condition when compared to both physiological, secondary pain and primary pain. Indeed, secondary, physiological pain can induce some reaction but the reaction is promoted by pain. This never happens in migraine, where the parallel phenomenon is sometimes incorrectly called "reaction". The congruity of the label "parallel phenomenon" is completely justified by the evidence that vegetative phenomena and metesthesias prelude or accompany pain depending on intra-individual variables. Finally, migraine is a primary pain that deeply differs from any other primary pain. As a matter of fact primary pain such as trigeminal neuralgia or deafferentation pain is seldom related to metesthesias and complex vegetative symptoms.

Finally, whatever its nature, migraine is an unique pathology represented by the non-linear, parallel phenomena of sensory-painful signalling and vegetative symptoms. This implies that migraine is not Σ Pain, Metesthesias + Vegetative symptoms. Conversely, all the mentioned are parallel phenomena. Such a parallel relationship is unique to migraine attack.

Parallel phenomenon A: pain

Pain is non-physiological, i.e. non-secondary, in its nature. In fact: (i) we cannot detect any injury as it is needed for secondary pain, and (ii) the needed ground for migraine is represented by hyperalgesia state [9] which is known to be due to central changes even when initiated by a peripheral event [10]. We stated that a "prone to pain signalling" state, currently named "hyperalgesia state" is inherited by following Mendelian law [9]. It seems obvious to state that the concept of inheritability is opposite to the possibility that pain is due to an exogenous nociceptive stimulus. That pain is primary in its nature means that its mechanism acts in the central nervous system (CNS) and implies the activation of second pain transmitting substances, like excitatory amino acids known to have a pivotal role in hyperalgesia state [11]. Regarding genetic features, we can say that the primary pain called migraine can be inherited. We also know that the proneness to such a painful disease is linked to the inheritability of hyperalgesia state [9]. One of the main features of migraine pain is its automatic, spontaneous onset that indicates the need for a factor having the role of a "releaser of automatic onset".

Parallel phenomenon B: reaction – its interpretation and translation into passive reaction

Itemizing "vegetative" features and metesthesias of a migraine attack, we can list a pivotal series of invariant signs, namely nausea (and vomiting), asthenia often indicating marked weakness strictly associated with mild breathlessness sensation and pre-cordial oppression.

Together, these signs mirror the phenomenology constellation of passive defence as observed in the animal [12, 13]. Passive defence is proper of some species of animals that react to a sudden attack by means of an automatic, predisposed reaction consisting in a death-like complex behaviour.

In case of a severe migraine attack, the vegetative symptoms and metesthesias mirror the pattern of a passive defence reaction. The relevant difference consists in the lack of any aggression. So, we can write Migraine = Pain parallel to Passive Defence Reaction. Nevertheless, here the attacker is absent, so we have to write:

Passive Defence Reaction - Defence = i.e. Pain, Passive (Reaction) Defence Phenomena.

Here, we underline that passive defence phenomena are no longer to be considered a reaction either to attacker or to pain but a parallel, non-linear phenomenon. The two parallel phenomena (pain and passive defence) seemingly appertain to categories entangled because of their origin in discrete areas of the CNS; moreover, they both are led by an overlapping pool of neurotransmitters. We can list their common features: biochemical feature, excitatory amino acids, acetylcholine [12, 13]; anatomical level, CNS from periaqueductal grey to limbic structures [12, 13]. The congruities linking pain and passive defence phenomena can suggest they appertain to an only group of "Group Theory Math".

Finally, the parallel phenomena represented by pain and passive defence result in a unique pathology named migraine that represents a absolutely new pathology.

Hypothesis of a "mechanism system" acting for migraine

Neurobiochemical, receptor activation/inhibition data, CNS levels of activity or depressed function, and peripheral receptor inhibition/activation may be considered input data. Output data are those clinically evident during the great migraine attack. By giving input and output data, we can obtain the rules of the system acting to evoke the observed output data. It seems obvious that such a system cannot be represented by a simple mathematic equation. Conversely, it ought to be represented by using several experimental curves and diagrams to obtain interpolate points.

Mathematical modelling of the concept of hyperalgesia and "automatism of primary pain", an output data set

As stated previously regarding the parallel phenomenon pain, also the parallel phenomenon passive defence is automatic and spontaneous in its nature. This indicates the need for a still unknown "releaser of automatic onset" of migraine - where migraine is pain paralleled by passive defence. In this case, "automatism" regards not only pain but the "entire migraine programme", i.e. Pain--- Passive Defence Phenomena.

Automatism is a term used currently for roughly indicating the breaking off of a condition in absence of an evident adequate stimulus, which is the stimulus commonly known to provoke the observed response. In medical science, the absence of an adequate stimulus compels physicians to define "automatic response" a condition that, in spite of the lack of any evident stimulus, mirrors a state induced by an adequate stimulus. This seems to be an incorrect concept. In fact, mixed maths learn that it is incorrect to hypothesize that only an established non-variant stimulus can induce a reaction. This is evident in the concept of "fatigue strength" which can be summed up as follows: every system has its own "breaking load" that is fixed and non-variant only in case the load is constantly applied, i.e. a tonic load. Conversely, the breaking load diminishes in case it is cyclically applied, i.e. in case of time-depending load, that is in case a "cyclic load" is applied [14]. The duration of the time-interval between two subsequent cyclic loads, may be also relevant. The load needed to meet the "breaking point" diminishes along with the increase of fatigue cycles [14]. So, the break is induced by a time-dependent load, usually represented by a sinusoid pattern function. The phenomenon can be represented by means of Wohler curve, as represented in the top curve of Fig. 1. Here, pain varies from 0 to a hypothetical value named D. In the curve, number of cyclic loads = 0 represents the condition we can indicate as "stat-

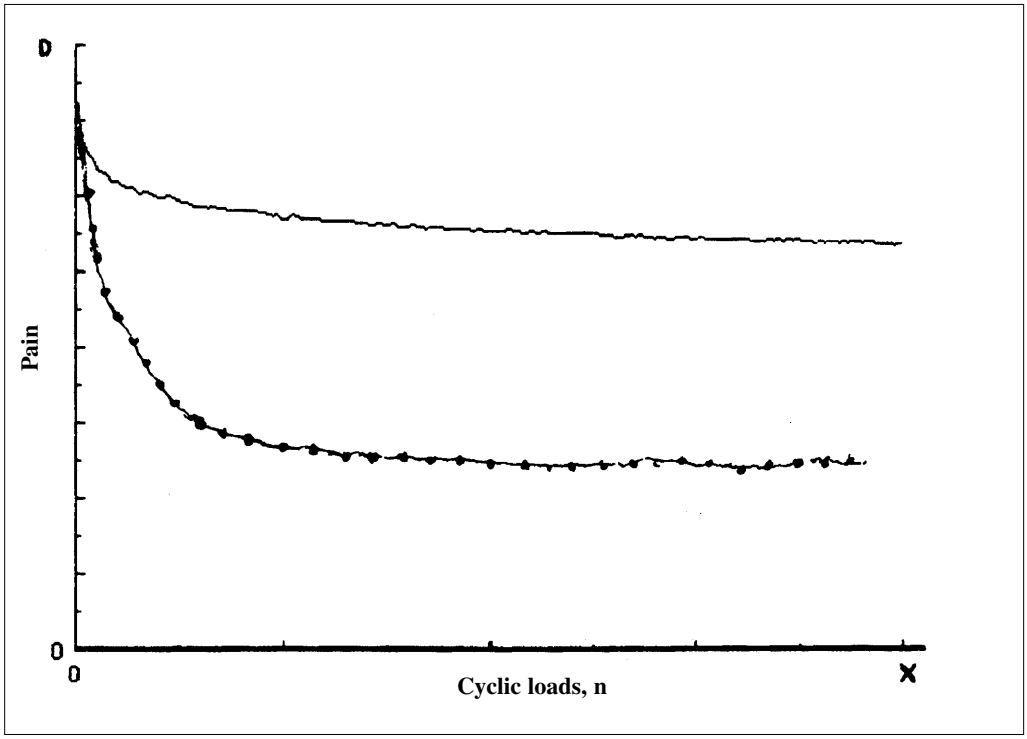

Fig. 1 A Wohler curve establishing that the breaking point of pain transmitting and inhibiting system can depend on both the severity of pain (load) and number of cycles of stimulation. *Continuous line* represents healthy pain transmitting and inhibiting system. *Dotted line* represents a "fragile" pain transmitting and inhibiting system. Here, load is represented by pain, the value of which varies between 0 and D

ic". It seems obvious that the breaking point of the system is less as the value of pain is more; in the same time, the breaking point is less as the number of cyclic loads is more [14]. The represented diagram gives us a law that establishes these variations and relationships.

It is noteworthy that, under a certain value of pain severity, the curve is asymptotic. This means that an under-threshold pain as well as an under-threshold cyclic load application of the pain itself will not change the functions of the system. The curve represented in Fig. 1 can be used to represent the pattern for inducing a disruption of pain/analgesia homeostasis. The system disruption induced by a cyclic load represents the pattern of both "first" and "secondary" hyperalgesia states [15, 16] which are induced by iterative, painful stimuli acting as disruptive factors in a physiologically well regulated sensory system.

We previously demonstrated an inheritable, genetic "third hyperalgesia" which follows Mendelian law and characterizes consanguineous migraine sufferers [9]. This compelled us to focus our attention on the fact that, here, the system is defective. The occurrence of a defect does not change the profile of the Wohler curve modelling the disruptive effect of a cyclically applied load. Nevertheless, a genetic defect implies the application also of the mechanical rule of "notch effect" (Fig. 1, bottom curve) that is known to induce a substantial decrease in the cyclic load capable of collapsing the system. Thus, an under-threshold stimulus, cyclically applied, can induce a "crack" in the system which acts for a tonic inhibition of the "broadcasting" of the entire "migraine programme", i.e. Pain --- Passive Defence. This is the "releasing event for automatism". That the needed stimulus is an under-threshold stimulus accounts for the "apparent" automatism. In fact, an observation which does not take into account the need for a stimulus different from the physiological one (Fig. 1, top curve) gives no explanation for the stemming off of pain that will seem to be "automatic", i.e. arising without a stimulus. In case there is a genetically determined "notch" in the system, the "resistance to fatigue" of the system itself will be highly influenced. Indeed, the breaking effect will occur following a cycle of stimuli having features different from the ones established for evoking the same effect in a physiological state. Thus, pathology differs from physiology only because of the fact that the breaking stimulus differs from physiological pattern as regards the time-load need to induce the effect (Fig. 1, bottom curve). So, the concept of "automatism" has to be substituted by the concept of "under number of cycles - under load stimulus".

Regarding genetic factors for proneness to primary pain, it is also noteworthy that notch effect indicates that breaking effect acts maximally near to "defect area" [14]. After the crack has initiated, a "crack propagation" occurs (Fig. 2). The parameters regulating such a crack propagation represent a major concern as regards the rules leading to a worsening of migraine: a disease based on a genetic defect of the analgesia system, i.e. by a notch in the material constituting the pain transmission and inhibition system.

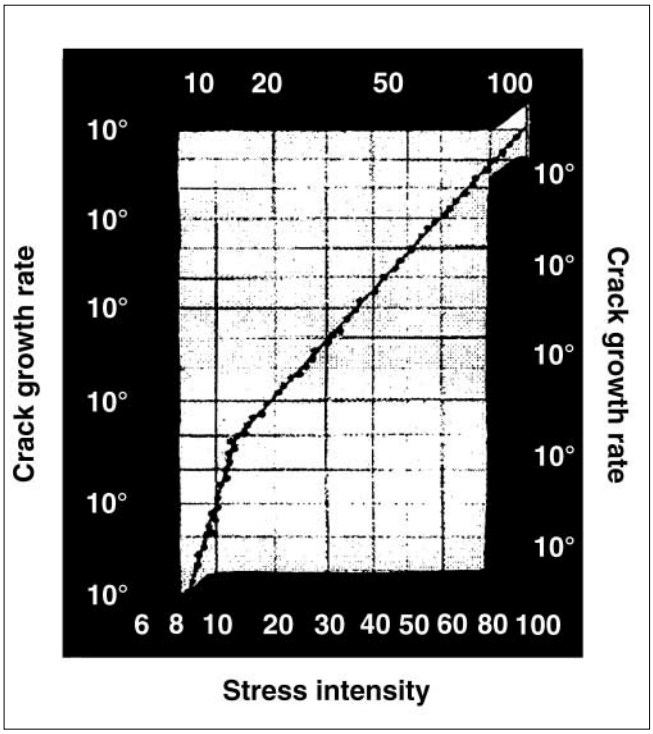

Fig. 2 Crack initiation data is vital to the stemming off of a genetic, inherited disease such as migraine. Nevertheless, the behaviour of the "migraine software system" after a crack is initiated is a major concern as regards time-related evolution of migraine itself. The image shows one type of crack propagation involving a crack growth per load cycle. In the chosen example, the measurement of cyclic load is simultaneous to measuring the change in crack length for a given number of cycles. Indeed, the two measures seem relevant in migraine worsening and relief

The problem of restitution headache-free period

Previously, we observed that a receptor's super-sensitivity to several monoamines, chiefly serotonin, occurs when the migraine attack is near to the end [17]. This means that migraine pain induces definite intracellular molecular reactions regarding neurotransmitters and receptor expression. These changes can recreate the lost equilibrium, so possibly diminishing the crack propagation. In this case a sinusoid pattern may occur in migraine syndrome. Our hypothesis is that such a restitution to equilibrium critically acts by temporary diminishing the crack effect as well as the crack length for a given number of cycles (Fig. 2). The data are

critical either as regards molecular medicine provision, or to a "decision". Indeed, we have to hypothesize the trend to the extension that is a constant in case that a notch effect. In this case, the extension changes either by increasing the sensitivity to fatigue or by changing the rules which regulate the sensitivity to fatigue, i.e. the sensitivity to sensory inputs and neurotransmitter challenges.

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