Migraine: its multiple facets

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The different forms of migraine make this pathology difficult to detect and treat. Jean Schoenen and his colleagues have discovered that, depending on their mitochondrial fingerprint, people affected by this illness do not respond in the same way to vitamin B2 treatment. Their study has been published in the Neurology journal.

It interferes in various forms with the life of over one person in ten and provokes long and incapacitating attacks in its victims. 'It' is migraine. If this illness, which affects three times as many women as men, is 'famous' for the headaches it causes, migraine is characterised by four main criteria established by the International Headache Society (IHS). These criteria enable in particular a distinction to be made between this pathology and headaches which have other causes.

A diagnosis of migraine is made when there have been at least five headache attacks which have lasted from 4 to 72 hours without effective treatment and in which at least two of the following characteristics appear: unilaterality, pulsatility, moderate to severe intensity and/or aggravation of the headache by physical activity. In addition, people affected by migraine have at least two of the following symptoms during the attacks: nausea and/or vomiting, photophobia and phonophobia, in other words a sharpened sensitiveness to light and sound. 'Around 16 to 18% of the population suffers from migraine attacks and for a fifth of this proportion the headache is preceded by essentially visual neurological disorders,' points out the ULg's Professor Jean Schoenen, director of the Headache Research Unit (Department of Neurology and GIGA-Neurosciences). 'It is what is known as a migraine with aura,' he specifies.

On what basis does migraine choose its prey? Its DNA! It is in the rare subtype called familial hemiplegic migraine that the first gene mutations were discovered. Nevertheless, frequent migraines, in the plural form, as in reality there exist several types and subtypes, are polygenic illnesses, in which the special features of several genes combine to determine the degree of susceptibility to cause the illness. In this way, thanks to our genetic heritage, each of us has a given 'migraine threshold.'

An excessive consumption of energy

'The migraine threshold depends on two things in particular: the reactivity of the nervous system to stimulation and the ability of mitochondria to produce energy,' explains Jean Schoenen. 'In migraine affected people we notice the absence of the habituation of the nervous system to external stimuli. If, for example, the patient is exposed in a repetitive way to a noise, to a light or to skin stimulation, the brain's reaction to this stimulus will not diminish over time, as it does in a normal person, and it even increases,' continues the Professor. Incapable of distinguishing between stimuli which are worth paying attention to and those of lesser importance, the brain reacts in an excessive manner to the latter, which prevents it from economising its energy.
As for the ability of mitochondria to produce energy in the form of ATP (adenosine triphosphate), Italian and American scientists demonstrated a few years ago, thanks to the nuclear magnetic resonance spectroscopy technique, that this ability is reduced by 20% in between migraine attacks. The result: 'It is as if we had a car fitted with a big motor which can reach very high revs but is equipped with a tiny petrol tank,' compares the neurologist. It is this imbalance between an excessive expenditure and a defective energy production in the brain that can cause migraine attacks.
Following up on these observations, Jean Schoenen in 1998 designed a study into the effectiveness of vitamin B2 in the preventative treatment of migraines. This vitamin is known to be an important cofactor in the mitochondrial electron transport chain (or oxydo-reduction chain, or mitochondrial oxidative phosphorylation chain) through which ATP molecules are produced, thus providing cells with energy. The clinical study carried out with the help of the members of the Belgian Headache Society, also published in the *Neurology* journal at the time, showed that administering strong doses (400mg) of vitamin B2, also known as riboflavin, had a preventative effect concerning the occurrence of migraine attacks. The frequency and intensity of the attacks had significantly decreased for 58% of the patients treated. And why not in the remaining 42%? That is the question the scientists asked themselves and, to try to answer it, Jean Schoenen at first considered measuring through spectroscopy the stocks of mitochondrial ATP before and after the patients were treated. But the experiment could not be carried out for reasons of developing the technology.

**A close up of the 'mitochondrial fingerprint'**

Professor Schoenen and his colleagues thus turned to Italian collaborators specialising in mitochondrial genetics at Rome’s 'La Sapienza' University. Mitochondria are intracellular structures bounded by a membrane and contained in the cytoplasm of eukaryotic cells. They are genuine power stations which recuperate the energy supplied by organic molecules which originate from digestion and stores it in the form of ATP molecules, the cells main source of energy. An important characteristic of mitochondria is that they possess their own genetic material: mitochondrial DNA. The analysis and sequencing of the mitochondrial genome are often used in phylogenetic analysis as well as in detecting genetic diseases linked to gene mutation in the mitochondrial DNA, where we thus talk of mitochondriopathies.

'With the help of the Italian researchers, we wanted to see if there was anything in the mitochondrial genome which identified the patients who responded to vitamin B2,' continues Jean Schoenen. Up until now the scientists have found no mutation in the coding sequences of mitochondrial genes to which could be linked a heightened susceptibility to migraines. Jean Schoenen and his colleagues thus decided to pore over the non-coding sequences of these genes. Within these regions it happens that a nucleotide, the basic structural unit of DNA, is replaced by another. The group of people as a whole who possess the same variations of nucleotides form what are called in scientific jargon a mitochondrial haplogroup. These people thus have the same 'fingerprint' in their mitochondrial genome.

For this new study (1), recently studied in the journal Neurology, 64 migraine sufferers were treated with riboflavin for four months. Over the course of the treatment, Jean Schoenen and his team noted the frequency of their patients' migraine attacks. The treatment was considered effective when a decrease of at least 50% in the frequency was observed. Blood samples taken from the patients were in addition sent to the Italian laboratory in order for their 'mitochondrial fingerprint' to be analysed. The analyses were carried out by researchers at the laboratory to whom no information about the patients or their response to the treatment had been given. The aim was simply to determine to which mitochondrial haplogroup each patient belonged.
Within the framework of this study, it was particularly interesting to distinguish two large groups of patients: those belonging to mitochondrial haplogroup H and those belonging to other haplogroups. "The people who make up haplogroup H have in principle a better mitochondrial metabolism. It is the most common haplogroup in Western Europe," points out Jean Schoenen. "People who belong to other haplogroups have a slightly weaker mitochondrial metabolism, characteristic of Asiatic peoples."

In comparing the analysis of the mitochondrial genome of migraine suffering patients and their response to vitamin B2 treatment, Jean Schoenen and his team were able to establish a link: "The majority of the people for whom the treatment proved effective did not belong to haplogroup H," specifies the neurologist. It remains to understand what that means from a biological point of view. The interpretation proposed by Professor is the following: "the people with haplogroup H did not respond to riboflavin because their mitochondrial metabolism is optimal. On the other hand, the representatives of other haplogroups, having less good energy engine rooms, which can thus be improved, were more inclined to respond to this treatment." Thus, in increasing the intake of vitamin B2, a cofactor in the mitochondrial phosphorylation chain, the treatment thus allowed the power station to optimise its production of energy for the cells of migraine affected patients. Certainly this is up until now just a hypothesis. To verify it it would be necessary to measure the patients' mitochondrial metabolism before and after being treated with riboflavin.

(1) C. Di Lorenzo, MD, F. Pierelli, MD, G. Coppola, MD, G. S. Grieco, PhD, C. Rengo, PhD, M. Ciccolella, BSc, D. Magis, MD, M. Bolla, MD, C. Casali, MD, F. M. Santorelli, PhD and J. Schoenen, MD., Mitochondrial DNA haplogroups influence the therapeutic response to riboflavin in migraineurs. Neurology, 2009;72:1588-1594

On the trail of the origins of migraine

As was mentioned earlier, the migraine threshold depends on, beyond the ability of mitochondria to produce energy, the nervous system's reactivity to stimuli. If belonging to different mitochondrial haplogroups can
explain why certain people respond better than others to vitamin B2 treatment, many unknowns remain concerning the mechanisms inherent in the appearance of migraines and the way treatments known to be effective against this illness work. At this stage Professor Schoenen plans to carry out the same type of study as that carried out for riboflavin for other medicines in order to better understand how and why certain migraine sufferers are more receptive than others to these medicines.

Another research project would also consist of furthering our understanding the way vitamin B2 acts on patients' energy metabolisms. 'With Austrian researchers we would like, amongst other, to check if people who respond effectively to riboflavin treatment have a basic deficiency of this vitamin,' explains Professor Schoenen. 'We do not think that we are making up for a vitamin B2 food intake deficiency in administrating 400mg to patients, as this dose is generally below the dose consumed naturally by humans, and smaller quantities do not work,' he continues. Another mystery which thus remains to be solved... 'Eventually, the ideal would be to be able to determine, thanks to rapid and not very costly genetic analyses, the genotype of migraine affected patients in order to prescribe them treatment adapted to their pathology,' concludes Jean Schoenen.