Editorial committee 2018

Chief editor: Dr. en C. Ildefonso Rodríguez Leyva
editor@revmexneuroci.com

Co-editors: M.C. Carolina León Jimenez
Dr. en C. Antonio Arauz Góngora
co-editor@revmexneuroci.com

Founding editor: Dra. Lilia Núñez Orozco
Emeritus editor: Dr. en C. Carlos Cantú Brito

National editorial comitee

Dr. Sergio de Jesús Aguilar Castillo
Dr. Marco Antonio Alegría Loyola
Dra. Alma Yolanda Alvarado Gutierrez
Dr. Carlos Gabriel Ascanio Rodríguez
Dra. Catherine Boll Woehrlen
Dr. Antonio Bravo Oro
Dr. Jorge Burgos Centeno
Dra. Graciela Cárdenas Hernández
Dr. Paul Carrillo Mora
Dra. Teresa Corona Vázquez
Dra. Beatriz Chavez
Dr. Bruno Estañol Vidal
Dra. Agnes Fleury
Dr. José Flores Rivera
Dra. Silvia García
Dr. Fernando Góngora Rivera
Dra. Margarita González Cruz
Dra. Alejandra González-Duarte
Dr. Oscar González-Vargas

Dr. Rubén Haro Silva
Dr. Juan Calixto Hernández Aguilar
Dr. Héctor Gerardo Hernández Rodríguez
Dr. Jesús Higuera Calleja
Dr. Javier Jaramillo de la Torre
Dr. Humberto Juárez Jiménez
Dr. Rubén Martínez Hernández
Dra. Iris E. Martínez Juárez
Dra. Adriana Martínez Mayorga
Dr. Francisco Mena-Barranco
Dra. Roxana Millán Cepeda
Dra. Rebeca Millán Guerrero
Dr. Alberto Mimenza Alvarado
Dra. Leticia Munive Baez
Dr. Luis Manuel Murillo Bonilla
Dr. Alfredo Ponce de León
Dr. Guillermo Ponce Bravo
Dra. Sandra Quiñones Aguilar
Dra. María Teresa Reyes

Dra. Mayela Rodríguez Violante
Dr. Leopoldo Rivera Castaño
Dr. Ulises Rodríguez Ortiz
Dr. Francisco Rogel Ortiz
Dr. Luis Ángel Ruano Calderón
Dra. Angélica Ruiz-Franco
Dr. José Luis Ruiz-Sandoval
Dr. José Manuel Sandoval Rivera
Dr. Daniel San Juan
Dr. Horacio Senties Madrid
Dra. Mónica Sierra del Rio
Dra. Ana Luisa Sosa Ortiz
Dr. José Luis Soto-Hernández
Dr. Gersain Trujillo Alonso
Dr. Steven Vargas Cañas
Dr. Rubén Dario Vargas García
Dra. Karina Vélez Jiménez
Dr. Marco Zenteno Castellanos

International editorial comitee

Dr. Anthony Amato
Dr. José Biller
Dr. Andre Kanner
Dra. Farrah Mateen
Dr. José Merino

Dr. José Obeso
Dr. Julio Pascual
Dr. Marc Patterson
Dra. Eduardo Tolosa

Statistical Advisor  Héctor Gerardo Hernández Rodríguez
Style corrector  Maestro Alejandro García
Translator  Rebeca Barroso
Design  Design Cortex
Contenidos

EDITORIAL
• Carta Editorial, Dr. Ildefonso Rodríguez Leyva

CONTRIBUCIONES ORIGINALES
• Placebo, nocebo y ningún tratamiento
• Electroestimulación y ejercicio de Williams en el tratamiento de la hernia de disco lumbar
• Estudio clínico y electroencefalográfico en lactantes con factores de riesgo de daño neurológico
• Frecuencia de la lesión medular pediátrica en un centro de rehabilitación. Experiencia de nueve años

REVISIONES
• Anticuerpos monoclonales contra el CGRP para el tratamiento de la migraña crónica y episódica
• Neurobiología de la percepción de las jerarquías sociales: revision actual de la literatura
• Patrones electroencefalográficos periódicos: un hallazgo controversial e infrecuente
• Neuronavegación: neurocirugía guiada por imagen
• Etiología, fenomenología, clasificación y tratamiento de la distonía

REPORTES DE CASO
• Hematoma remoto cerebeloso post-fibrinolisis

Contents

EDITORIAL
• Editorial letter, Dr. Ildefonso Rodríguez Leyva

ORIGINAL CONTRIBUTIONS
• Placebo, Nocebo and no treatment
• Electrostimulation and exercise of Williams in the treatment of lumbar disc herniation
• Clinical and electroencephalographic study in infants with risk factors for neurological damage
• Frequency of Pediatric Spinal Cord Injury. 9 years experience

REVIEWS
• Anti-CGRP Monoclonal Antibodies for the Treatment of Chronic and Episodic Migraines
• Neurobiology of the perception of social hierarchies: current revision of the literature
• Periodic electroencephalographic (EEG) patterns: a controversial and infrequent finding
• Neuronavigation: Imaging-guided Neurosurgery
• Dystonia: Etiology, phenomenology, classification and treatment

CASE REPORTS
• Remote cerebellar haemorrhage after thrombolysis
Reflections for young neurologists

It is a privilege to be standing here before you and make some simple reflections.

Being a doctor is a privilege because it is the profession in which art and science come together as one, but also one in which the service to the society is implicit and the behavior of each and every one of us is public and will always be in constant vigilance by our society.

Being a doctor, and moreover being a Neurologist, implies serving as a researcher of the most astonishing organ that exists in the body. Every time we see a new patient we inquire, we look for evidence when exploring, we correlate in syndromes the symptoms and signs and we especially locate where the problem of the patient is, for then associating this location with the found semiology, and defining the most probable ethology and for avoiding errors by making a differential approach.

The Artificial Intelligence uses the algorithm as a method that will logically find the answer for the suffering that corresponds to the problem and to which treatment one would obtain the better outcome. This algorithm deduction has been used by Neurology practically since it was born. This is why Neurology is the most beautiful medical specialty, or at least that is how we who have decided to specialize in this area feel.

Young neurologists; each new generation must be better than the previous one; just as children must be better than their parents and students better than their teachers. It is up to you to spread into others the passion for this art, for this science. You will probably not be as rich as some businessmen, but you will never lack the work, you will never fall into boredom, you will never not have anything new to study and you will always have the chance to learn something new.
Perhaps many times you will feel worn out or tired and you will probably face failure and impotence, but be sure that with an honorable job, you will provide welfare to your family and in each consult you will have the opportunity to research what your patient suffers, of educating them and their family, of preventing them from other illnesses and of even charging for a dignified and fructiferous work.

I wish to you that success does not make you arrogant, that ambition does not make you petty and that power does not blind you. I wish that you serve the poor and the rich, the simple-hearted and the powerful, the unkempt and the well endowed and above all generic preferences, that you serve with the honest desire to serve and to give back wellbeing to those who are coming to you for support.

Be the very best to your possible extent, and know that there will always be someone next to us from which to learn and someone next to us for us to teach. Build a better country and better your surroundings, because even if there is a lot to do and not a lot of time to do so, however little or much we are able to achieve will surely make a difference in our country, a country that is in need of more education, better health services and more justice.

Perhaps our reach is small, but be sure that every little thing counts and whatever you do will make a great difference.

Ildefonso Rodríguez-Leyva
Editor
Placebo, nocebo and no treatment

Placebo, nocebo y ningún tratamiento

Abstract

The far-reaching meaning of placebo and nocebo are often undervalued or ignored in clinical practice. Presently the term placebo is either used: (1) in the context of randomized controlled trials, (2) to describe a sham treatment in various nuances, (3) to describe effects often attributed to healers. This diverges from “no treatment” which has entirely different implications. Even less accepted is the term nocebo, which literally means “will harm”. As placebo this term can be ambiguous and can appear in many concealed ways. Research in the past years has been based on experiments and elaborated studies and on imaging studies. This both placebo and nocebo also have an empirical and scientific background. Also, ethical aspects concern placebo and nocebo issues, in particular in regard to changing relations of the physician-patient relationship, which affects both terms. Based on this knowledge, increasingly physicians and patients are aware of these phenomena, and it will be important to raise awareness not only in physicians, but also the health care personal involved in the treatment of patients.
Resumen

El significado de gran alcance de los efectos placebo y nocebo a menudo se subestiman o son ignorados en la práctica clínica. Actualmente, el término placebo se usa: (1) en el contexto de ensayos clínicos controlados aleatorizados (RCTs, por sus siglas en inglés); (2) para describir un tratamiento simulado en varios matices y (3) describe los efectos a menudo atribuidos a los curanderos. Esto difiere del "no tratamiento", que tiene implicaciones completamente diferentes. Aún menos aceptado es el término nocebo, que literalmente significa "que dañará". Como placebo, este término puede ser ambiguo y puede aparecer de muchas maneras ocultas. La investigación en los últimos años se ha basado en experimentos, estudios elaborados y en estudios de imágenes. El placebo y nocebo también tienen antecedentes empíricos y científicos. Además, aspectos éticos conciernen a los conceptos placebo y nocebo, en particular con respecto a las relaciones cambiantes de la relación médico-paciente, que afecta a ambos términos. Con base en dicho conocimiento, cada vez más médicos y pacientes son conscientes de estos fenómenos, y será importante concientizar no solo a los médicos, sino también al personal de atención médica involucrado en el tratamiento de los pacientes.

Palabras clave
placebo, nocebo, ningún tratamiento, mecanismos, ética

Correspondence adress:
Wolfgang Grisold, Dr. med., Univ. Prof.
Ludwig Boltzmann Institute for Experimental and Clinical Traumatology
e-mail: grisoldw@gmail.com
Introduction

The meaning and importance of placebo and nocebo are often undervalued or ignored in clinical practice and by Health Care Practitioner (HCP).

Presently the term placebo is either used in the context of Randomized Controlled Trials (RTC), or describing a “fake” or sham treatment, in different circumstances.

This is different from “no treatment” which has different implications, and also will be discussed in the paper, in particular as this can occur with or without consent of patients.

There is less awareness for the term nocebo, which means “I will harm” and is often considered a “bad prediction”. Like placebo also nocebo can appear many concealed ways.

The knowledge and the appreciation of the placebo effect is still in need of more dissemination, both in regard to physicians, medical personal and patients.

The scientific basis and evidence for placebo has dramatically increased in the past years based on sophisticated studies, the effects of placebo effects calculated in studies and imaging studies\(^1\) placebo and health,\(^2\) meaning;\(^2\) and psychiatric conditions\(^3\). It is important to acknowledge, that all drugs do have a placebo effects to some extent.\(^4\)

In addition to the need to raise awareness on placebo and nocebo in clinical practice, also ethical consideration and contextualization (“Zeitgeist”) are important. As an example, the meaning of placebo is presently different, than in the first half of the last century.

History

Medicine until the beginning of the 20th century to some extent has a history of placebo (P) (as the term is used now), as seen from contemporary medicine as standardizes pharmacological therapies were not available.\(^5\)

The effects of both P and nocebo (N) have been observed in ancient cultures. However, also the present distribution of health resources suggest that in 80 % of the world population medicine is not available, but persons are treated by traditional methods, herbs and healers, as demonstrated in a review on epilepsy.\(^6\)

In the middle ages the term of “Placebo” was reserved for professional mourners and had a continuous development until today. Well known are examples as Mesmerism and Perinism, (around 1700)\(^7\) which were at the time investigated and clearly demonstrated, effects which we would now term “Placebo”.

During the last century the meaning of P has undergone changes: until the second world war the application of P drugs, without the knowledge of patients, was accepted. The major change in doctor patient relationship has changed since.

At the same time the term of the term P has become an essential part of RTCs. Thus, the meaning of the term has shifted to a technical expression. It is also interesting, that the “meaning/value” of P is perceived differently by different professional groups.

Presumably basic researchers and scientists may have a low opinion on P, contrary to physicians and some HCPs.

What is a placebo?

Placebo is a term which needs further clarification and will be explained below:

1) Placebo is considered an inert therapy or “sugar pill”. The term “sham” refers to a similar effect but is usually combined with an intervention (eg. knee operations). A positive effect of the intervention is considered a placebo effect.
2) In an RTC, which is considered the state of art, in clinical studies, the placebo effect is always determined in the verum group and the placebo group; the difference is the therapeutic effect.

3) Placebo also refers to the relation of physicians and patients. This is not only the personal interaction, but also other circumstances of interaction and treatment. These circumstances are often defined as “rituals”.

4) The placebo effect is not only person dependent, but also depends on the disease: for example, diseases with natural fluctuations (e.g. Migraine, seizures), are associated with different placebo effects than a chronic progressive disease as PD or dementia. These are fundamental differences, which make the comparison of the placebo effects difficult.

**Table 1.** Placebo effect and factors to be considered.

<table>
<thead>
<tr>
<th>Natural course of the disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Regression to the mean”</td>
</tr>
<tr>
<td>Fluctuations</td>
</tr>
<tr>
<td>Doctor and patient bias</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The “Hawthorne effect” *</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Observer bias - patient bias</td>
<td></td>
</tr>
<tr>
<td>Patient learning and “unlearning”</td>
<td></td>
</tr>
</tbody>
</table>

* Hawthorne effect: the “Hawthorne effect” describes changes in behavioral pattern, in persons being observed.

**“No treatment” group**

The “No treatment” is not the same as placebo also there is some discrimination of the terms is necessary:

a) Is the patient informed that he receives no treatment?

b) Is he in a controlled study group?

c) Is it a historic comparison group

d) It is unacceptable to exclude patients from drugs, if a medication is available for the purpose of a study.

In RTCs usually a treatment group and a placebo group are compared. Presumably, also a “no treatment group” would be needed to exclude the interaction of the patient with the study team, when serving as an observer. It must be assumed, that even the information that this group will receive no treatment, might be a bias.

Examples of no treatment groups can be historical patient groups (for example the natural history of a disease before adequate treatment was available), patients not treated for other reasons or patients refusing treatment. There are also examples of patients which were deliberately excluded from already available therapies for the sake of investigation. An example of such a practice is are investigations on the natural course of syphilis.

This is an example of no treatment, and there are many ethical concerns involved.

**Is there a placebo patient?**

The identification of a “placebo patient” is seen controversially and is aimed to identify patients in regard to their inclination to have a placebo response. This discussion is controversial, and also touches genetic aspects.

The potential response towards placebo could also be depending on the type of the disease. As examples depressive disorders seem to have a high placebo response than other diseases (see below).

Cultural influences also need to be considered and are important in dealing with patients, who have another cultural background. In particular pain and pain tolerance vary in different cultures. Issues of migrants are becoming increasingly important as the individual spectrum may vary.
Inherent factors influencing the placebo effect:

The P effect has several components. Expectation, conditioning, and observational learning are important key words in placebo, which will be discussed below.

a. Expectations
Expectation is an important and essential part/dimension of/in placebo. The expectation of an event can be very powerful and can exert a main influence on the placebo effect. Additionally, age, social, observational and cultural aspects also seem to have an influence.

A daily life example is “wine tasting” by experts, where the expectation of the wine tasters can be influenced by factors stimulating their expectation. Two groups who were served expensive and cheap wine following the announcement of the quality of the wine were not able to distinguish between the two types.

In a similar experiment 2 groups been given regular and decaffeinated coffee. After several interchanges between the two groups also in this case accurate distinctions could not be made.

b. Conditioning
Conditioning is best explained by Pavlov’s dog experiments. Upon the ringing of the bell hypersalivation sets in. In a similar way/pattern, medical procedures and rituals may condition for upcoming experiences. The type of effect of the same procedure in different patient population could be related both to expectations and conditioning.

The perception can be influenced by prior experience, fear and anxiety, reward expectations, motivation, the wish for improvement or amelioration, as well as cure in both the placebo and the serum drug/procedure.

c. Observational learning
Means that patients and relatives learn from one another. This means that positive effects as placebo or the reverse can be elicited. A famous term is the “Hawthorne effect”. This observation was made in an industrial environment; however, it can be compared to the patient-physician relationship.

Are there scientific results explaining the placebo effect?

There is increasing evidence and literature, for biological effects of placebo. Some mechanisms are summarized on Table 2.

Important issues in the P and N effect are functional MR investigations, which help to identify neuronal networks. Investigations demonstrate functional MR changes occurring during placebo effects.

The issue of similarities between “verum” drug treatment and placebo was described in studies.

Another interesting question is whether the knowledge that the study contains placebo arm, also influences the result of the study.

There are many other questions and topics related to placebo, which have been summarized in published works.

The mechanisms of placebo effects are also subject to several items relating from psychological effects towards biochemical and receptor-based assumptions: The P effect was also studied in regard to learning frames and behavioral patterns and whether the awareness of possibly receiving a placebo also influences the study.

Table 2.

<table>
<thead>
<tr>
<th>Psychologic phenomena</th>
</tr>
</thead>
<tbody>
<tr>
<td>The endogenous opioid system</td>
</tr>
<tr>
<td>The endogenous cannabinoid system</td>
</tr>
<tr>
<td>The cholecystokininergic system</td>
</tr>
<tr>
<td>The dopaminergic system</td>
</tr>
</tbody>
</table>
The placebo effects vary in different diseases:

Placebo effects appear in different shapes and manifestations in different diseases. This can be explained by the characteristics of the disease. Episodic diseases must be compared with chronic progressive diseases, where the placebo effect has different dimensions. Also fluctuations, spontaneous remissions and “regression to the mean” and the effect of the physician patient relations are important. For neurological diseases, the placebo effects will have distinct and varying patterns in migraine, neuralgia and chronic progressive diseases as Parkinson syndrome.

For several diseases as endocrine dysfunctions, gastrointestinal disorders, long and respiration disorders, autoimmune diseases, chronic pain syndromes investigations to determine the P effect have been made. In particular in cardiovascular diseases many studies are available.

Placebo is not exclusively connected with drug treatment, but is inherent to other interventions as knee surgery, the well examined operation of internal mammaria artery, and in regard to the disputable sham surgery.

Placebo controlled studies can be difficult in vulnerable populations as children, psychiatric patients, geriatric patients and dependents for other reasons.

The physician and HCP as a placebo

The relation of patients with physicians and HCP are important factors and contribute to the P and N effect. It is important that, independent of the acknowledgement of P and N, any relation between patients, therapists and carers implicitly contain a placebo or nocebo effect. It is important to raise the awareness of the issue among the HCP.

Empathy and “compassion”

The terms empathy and compassion are often used in a similar context. Empathy describes the ability to be able to affectively deal with emotional aspects. Further distinctions are made between verbal and cognitive empathy. Empathic behavior can also be observed in the prescription behavior of drugs.

The term Compassion describes the “co-suffering” which also animates to provide emotional help. “Compassion fatigue” is usually considered a sign of exhaustion and may be similar to what is considered a “burn out” syndrome, which is an ambiguous and multi-contextual term which many be traced to Graham Greene's book “A burnt out case”.
Other terms, which have closely related meanings, such as sympathy, an emotional reaction towards the misfortune of others, especially those who may suffer “unfairly”,28 and “passion”29 are used to describe attitudes and relations with patients.

“Grooming”

Grooming which defines the care for one’s appearance, is used as auto- or also allogrooming and employed in the nursing literature. It describes a social behavior, including intensive social contacts, consisting of empathy, compassion, eye contact and haptic sensations. The grooming of the patient by the HCP and, in particular, the physician can also provide a reciprocal reward for the HCP and is infrequently mentioned.30

“Trust”

Trust is a cornerstone of the relation between HCP and patients. In addition to psychological explanations, also the circuit of the amygdala and the effects of oxytocin seem to play an eminent part. Interpersonal factors, as relationship, the appreciation of the HCPs work or often admiration for physician’s work play an important role and may enhance trust.

The Nocebo effect

Conversely to placebo, the meaning of the term nocebo is practically less commonly used, however, it may be of equal importance. Translated its meaning, the term suggest: “I will harm”, which is probably not always the intention.

The intentional use of nocebo is rare, but not impossible. However, one can assume that usually the attitude of physicians and HCP rather strives for a placebo effect. Sometimes a nocebo effect can be interwoven in the placebo response.31,32 Examples are Placebo controlled trials, where persons on placebo develop side effects of the verum group, which cannot be expected from the inert placebo and are presumably induced by studying the description of the possible side effects.

Fear, worry and anxiety can predispose to negative expectations. The phenomenon of the negative prediction has also been observed as a cultural phenomenon in the “Voodoo” acts.33

More trivial, but important in a large number, are possible negative predictions contained in manufacturer’s instructions for medications.34,35 The information is often unweighted and not listed according to frequency and the impact of the side effect. Often patients are then distracted from the main effect of the drug, and experience the nocebo effect as side effects.36,37

Nocebo can also be induced by negative comments or non-appreciative behavior of the medical personal towards the patient as well as carers. Disrespect, negatively formulated statements, lack of attention and mindfulness are examples.

Placebo-Nocebo: Hope or euphemism?

The present concept of patient relation is based on autonomy and partnership. Compared with the prior paternalistic concept of physician – patient relations, the confrontation of severely sick patients has been avoiding prognosis and the discussion of death.

The physician is often confronted with hope and euphemisms. Hope for the sick patient is not always the hope for cure, but the amelioration of symptoms, reduction of pain, disappearance of nausea, or some personal issues, as meeting members of his family38 as well as settling important personal issues.

The doctor/nurse as a patient?

Mostly, the self-experience of disease in the HCP is lacking. This is particularly relevant in the case
Ethical aspects:

Ethical attitudes and opinions are subject to time changes and contextualization. Until the 1960s the prescriptions of inert drugs as placebo were tolerated and at times even encouraged. This has changed and presently there are severe concerns that this practice would be considered as a deliberate deception of the patient.39,40,41

However, in addition to this rather clear defined aspect, there are some sliding and more vague aspects regarding placebo, for example, prescribing a drug in a lower dose, using an off-label drug, as well as lacking adequate knowledge on the drug effects which were described.

Self-responsibility also includes increased self-medication. This depends on the region of the world and to the access of drugs. The literature search for this problem was not revealing significant work on this focused problem, except in psychiatric disorder and addiction.42

The “golden standard” is often discussed in the debates of ethic boards, i.e. “The best or most successful diagnostic or therapeutic modality for a condition, against which new tests or results and protocols are compared”. However, the study results are based often on a small margin between the effect of the therapy and the placebo effect. Frequently, statistical finesse is needed to substantiate this effect.

No treatment seems be unambiguous. However, “no treatment” can be done with consent of the patient and is not acceptable for study reasons, if some kind of treatment is already available and is, thus, denied to the patient. The example of the Tuscaroo event,9 where penicillin was denied to patients to study the natural course of the syphilis disease is deplorable.

Can placebos be used with the knowledge of the patient that he is receiving a placebo? Yes, this can occur and has been practiced under the term “undisguised placebo”. A good example is the sale of OBECALP (which is the reverse spelling of Placebo). (https://blogs.webmd.com/all-ears/2012/07/placebos.html). In this case, the patients and carers are informed that the prescribed drug is inert.

Another similar example comes from a psychiatric scenario where a patient with a depression received a placebo during a study and improved. After the study the result was revealed to the patient, and the prescription of the verum was offered. He refused on the ground that the drug he had received was successful.

In RTCs, the P treatment is part of the current concept; however, this procedure might be subjected to critique.43 Nevertheless, the RTC can be considered to a legitimate and approved method, also defined according to the Helsinki criteria.44

From the previous considerations, it is worthwhile to consider that placebo is an inert substance;
however, the large number of possibly associated circumstances as procedures, rituals and interaction, and possibly even the shape and color of the drug play an important role.

In summary, it is not easy to define the ethical aspects of P, however it seems easier to define concerning the N effects. Statements can include negative predictions: as an example, the medical information often distracts the patient from the aim of the prescription. However, there is also a small slope which is between a realistic and truthful disclosure, and a euphemistic information, which may spare the patient from the negative prediction, but may not be truthful.

The expectation of a patient in need is improvement or cure of his condition. This expectation is usually combined with hope.

Several investigations discriminate between placebo effects in different conditions. As an example, cancer pain in a progressive metastatic state will not have the same type of hope for healing. A transient disease, as headache or migraine may have completely different placebo effects, than a chronic progressive disease. In particular, periodically recurring diseases, despite severe and often debilitating symptoms, leave the hope for the patient for complete remission and improvement. Increasingly also alternative therapies are considered. Although still scarcely reported, also the placebo effect may play a role in advanced disease, and also palliative situations.

As P and N mirror the interaction of the patient with the HCPs, in particular the patient/physician relation, the effect is ubiquitous and not avoidable, and has to be taken into account in any interaction.

In practice the adherence of patients to autonomy and self-responsibility, may still include several uncertainties. True content can be transmitted in several ways: true content with emphasis of the negative aspects, a more weighted content trying to describe the content and the advantages and disadvantages, or a euphemistic approach. All three possibilities are “truth”-based but may have different effects ranging from nocebo to placebo or even deliberate deception. None of these three approaches is completely right or wrong. Often the wishes and needs of the individuals are not sufficiently considered.

Strictly speaking also therapies as alternative methods as AP may fall in the category of placebo and often these methods such as massage, physical therapies etc. are used and prescribed, however their effect is not proven in the conventional settings.

Vulnerable patient groups:

Some patient groups are vulnerable, meaning that they are, for some reason, unable to understand or give consent or are in some kind of dependency. These are children, psychiatric, geriatric patients and dependents such as members of organizations (eg. army) or prisoners, who for other reasons might not be able to give consent. This also has throwbacks as necessary studies in the vulnerable groups cannot be made. Possibly, new designs and comparisons of other parameters which were formerly used in the RTC, will help to enable investigations, and at the same time adhere to ethical principles.
Summary

This short review outlines the importance of placebo and nocebo in medicine. It also points out, that placebo has several meanings, from the study group in an RTC towards many other aspects of interaction of patients, carers and HCP. Contrary to placebo, the term nocebo is not well known, but of equal importance, yet the awareness is still less, and the theoretical background is also less explored. In addition to P and N also the meaning of “no treatment group” is important as it also includes a spectrum of different possibilities.

The changes in patient – physician relationship also has an influence on changes of the term and content of placebo. Yet, despite evidence based medicine, autonomy and self-responsibility of patients, placebo and nocebo are inherent parts of therapy.

The aim of this paper is to raise awareness for the manifold appearance of P, and also the awareness of N. This is important as both effects are continuously contained in our interactions.

Apart from the well formulated P effect in RTC, the ubiquitous P and N effects are a permanent part of our work.

Conflicts of interest
We declare that this research has no conflicts of interest.

Funding
No funding was received for the realization of this work.
References

33. Benson, H. Placebo, Nocebo and no treatment
Original contribution

Electrical stimulation and Williams exercises for the treatment of lumbar disc herniation

Abstract

Objective. To determine the decrease in pain due to lumbar disc herniation using electrostimulation compared to Williams exercises in patients attending the Social Security Institute of State Workers in Tabasco (ISSSTE) in May, 2016.

Material and methods. An observational, analytical, longitudinal, and prospective study was performed in patients with a diagnosis of lumbar disc hernia that came to the Social Security Institute of State Workers (ISSSTE) in May, 2016 with the objective of comparing the pain tolerance benefit of the Lumbar disc herniation in patients treated with electrostimulation and Williams exercise.

Results. Twenty-one patients with lumbar disc herniation treated with electrostimulation were evaluated, indicating an improvement in the tolerance to low back pain (p≤0.05).

Conclusion. The use of this electrostimulation offers an alternative for pain tolerance from the first clinical session.

Keywords
Low back pain, electrotherapy, rehabilitation, Tabasco.
Resumen

Objetivo. Determinar la disminución del dolor por hernia de disco lumbar mediante electroestimulación en comparación con los ejercicios de Williams en pacientes que asisten al Instituto de Trabajadores del Estado de la Seguridad Social en Tabasco (ISSSTE) en Mayo de 2016.

Material y Métodos. Se realizó un estudio observacional, analítico, longitudinal y prospectivo en pacientes con diagnóstico hernia de disco lumbar que acudan al Instituto de Seguridad Social de Trabajadores del Estado (ISSSTE) en Mayo del 2016 con el objetivo de comparar el beneficio de tolerancia de dolor de la hernia de disco lumbar en pacientes tratados con electroestimulación y ejercicio de Williams.

Resultados. Se evaluaron a 21 pacientes con hernia de disco lumbar tratados con electroestimulación, denotando mejora en la tolerancia al dolor lumbar (p≤0,05).

Conclusión. El empleo de esta electroestimulación ofrece una alternativa para la tolerancia al dolor desde la primera sesión clínica.

Palabras clave
Hernia de disco lumbar, electroterapia, rehabilitación, Tabasco.

Corresponding author:
Edgar García Rojas
Tel. 3-39-23-86
E-mail: edgarojas.89@gmail.com
Introduction

Lumbar disc herniation can be considered an adjacent mechanism for the release and alterations of biochemical compounds and not just from the inflammatory response, but there is also an increase in total cholesterol (p < 0.001) and low-density cholesterol (LDL) (p = 0.001). It is associated to certain causes such as male gender (OR: 2.93, 95% CI: 1.26-6.79, p < 0.05), age over 25 years, obesity, sedentary lifestyle, smoking (OR: 4.15; 95% CI: 1.59-10.83, p < 0.05), metabolic syndrome (OR: 1.66, 95% CI: 1.40-1.95, p <0.05), together with certain hard labor activities and driving motor vehicles (OR: 1.7, 95% CI: 0.2-2.7). The pathology can be seen from an age as early as 12 years, where a relative association with sports activities has been detailed.

Within the treatment alternatives, intervention with physiatric activities to relieve symptoms has been described. A sample of 22 subjects with disabling low back pain aged 51 ± 9.11 years who had two treatment sessions applied with interferential current, tetrapolar method, by means of 75 cm2 surface electrodes in a lapse of 25 minutes, showed an improvement in pain relief evaluated using the Visual Analogue Scale (VAS) (p = 0.017).

In a randomized group, nerve root block therapy in patients with herniated disc and physiatric treatment showed pain reduction compared to subjects without physiotherapeutic intervention, both with a follow-up of six continuous months evaluated with the Back Pain Disability Questionnaire and Pain Scale.

In addition to the above, various drugs applied as an epidural injection have been used to relieve pain in chronic spinal conditions, such as percutaneous discolysis with ozone.

In this area, the Yeung Nam University Medical Center evaluated pain reduction with gadolinium in 37 patients with radicular pain in the lower extremity, measured with the Disability Index Assessment Scale, denoting improvement after four weeks of follow-up (p<0.05) and with nerve root block in patients with herniated disc. If the conservative treatment is inefficient, the next step can be a laminectomy or facetectomy, with a surgical time oscillating around 4.29 ± 1.05 hours and a hospital stay of 9.09 ± 4.13 with a range of 1-20 days.

Therefore, the objective of this study is to determine the reduction of pain due to lumbar disc herniation through the use of electrical stimulation compared to Williams exercises in patients at the Institute for Social Security and Services for State Workers in Tabasco (ISSSTE) in May of 2016.

Materials y methods

An observational, analytical, longitudinal and prospective study was performed in patients diagnosed with lumbar disc herniation who attended the ISSSTE from May 2 to May 20, 2016 in Tabasco.

Obtaining a probabilistic sample for a finite population with a universe of 46 patients who agreed to participate in the study, with a confidence level of 95%, p=0.5 q=0.5, with a permissible error of 95%. Selected by systematic sampling.

We included individuals of legal age, with postero-lateral L4-L5 lumbar disc herniation who were diagnosed by anteroposterior and lateral radiography of the segment, as well as an MRI not older than three months at the time of the study. They had partial prolapse of the nucleus pulposus categorized as uncomplicated, lumbar instability associated with ligamentous alteration, no alterations on the skin or protuberances, previous spinal surgeries. Individuals with a history of chronic medullary involvement and diagnosis of previous medullary section or peripheral nerve involvement, dermatological lesions, chronic renal...
Results

Twenty-one patients with lumbar disc herniation were evaluated, of which 12 were female (57%) and nine were male (43%), received electrical stimulation (Figure 1).

Twenty-one patients, of which 12% were male and 88% female, received Williams exercises and were evaluated (Figure 2).

The VAS results are presented in Table 1. An assessment of 7.90 ± 0.831 was obtained at the beginning and 1.10 ± 0.181 at the end, indicating a statistically significant improvement in pain tolerance after the application sessions (p≤0.05).

Table 2 shows the comparison of the end results of the two types of treatment. The electrical stimulation group had VAS final scores of 1.10 ± 0.181 while the patients treated with Williams exercises had final scores of 3.19 ± 0.981, finding a statistically significant decrease in pain when applying electrical stimulation with interferential current in analgesic modality (p≤0.05).

At the beginning of the study, the patients who received electrical stimulation reported pain at a score of 8 points on the VAS scale, at five days of application they reported 5.61, at day ten a score of 3.57, and at day fifteen a score of 1.09. Those who opted for treatment with Williams exercises had 7.9 points at the beginning of the study, 6.95 at five days, 5.38 at ten days, and 3.19 at fifteen days with a significant decrease of pain after five days of therapy (p≤0.05) (Figure 3).
**Table 1.** Final VAS results of the subjects treated with electrical stimulation.

<table>
<thead>
<tr>
<th>Electrical stimulation</th>
<th>Mean ± Standard Deviation</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start (day 1)</td>
<td>7.90±0.831*</td>
<td>0.000</td>
</tr>
<tr>
<td>End (day 15)</td>
<td>1.10±0.181</td>
<td></td>
</tr>
</tbody>
</table>

*Student's t-test results.

Source: Electrical stimulation and Williams exercises in the treatment of lumbar disc herniation.
**Table 2.** Comparison of the final VAS results of the physiatric therapies.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean ± Standard Deviation</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrical stimulation</td>
<td>1.10±.831*</td>
<td>0.000</td>
</tr>
<tr>
<td>Williams exercises</td>
<td>3.19±.981</td>
<td></td>
</tr>
</tbody>
</table>

*Student’s t-test results.

Source: Electrical stimulation and Williams exercises in the treatment of lumbar disc herniation.

**Figure 3.** RVAS results of the patients at the beginning and at the end of the sessions of the physiatric therapies of electrical stimulation and Williams exercises.

Source: Electrical stimulation and Williams exercises in the treatment of lumbar disc herniation.

**Discussion**

Martínez Pintor in 2011 stated that interferential currents provide a series of important advantages, both for the patient and for the therapist. According to the results of our study, decreased back pain was observed with the use of electrical stimulation. The subjects treated for the first time with electrical therapy presented an improvement from the first session, while the patients who were given Williams exercises did not mention improvement on the first intervention. It should be mentioned that in order to observe more precise results in the use of rehabilitative techniques, the studies must be longitudinal. It is substantial to note, however, that an improvement in the patient’s clinical condition may be there from the outset by employing physical therapies that include technology, providing significant support to the physiotherapist’s exercises.

The electrical stimulation showed that, when applied from the start, it can contribute to the improvement of pain relief in those individuals where clinical conditions allow it. Zakharov & Shirokov in 2009 reported 22 patients aged 45.4 ± 6.2 years who underwent electrical stimulation for radiculopathy with compressions in L5 and S1 demonstrating the possibility that this therapeutic option optimizes the peripheral nerves. Comparing the results, there is an observable
decrease in pain perception from first contact and all the way through subsequent sessions.

Physiatric options aimed at reducing pain have a fundamental characteristic in relation to spinal cord compression: in the beginning, a musculoskeletal adaptation can influence improvement of the compression given that the relaxation of the muscles helps improve muscle tone, adequate contraction, and gradual decompression of the affected area.

Calvo’s study in 2012 at the Presidente Juárez Regional Hospital of the ISSSTE in Oaxaca included 26 patients diagnosed with lumbar disc herniation in L3-4, L4-5, and L5-S1 from July 2008 to June 2009. He implemented the use of interspinous spacers Lixus OXPEKK®-IG, reducing the pain according to the VAS from 8.7 at the start to 6.7 six months later, with a decrease of 0.5 points at month 24, reducing pain by 94%.23

Technology, with its wide range of alternatives, is very favorable in the treatment for pain relief, as long as whoever applies it takes into consideration the risks and benefits entailed and chooses the most appropriate one for their patient. An assessment of a group of subjects suffering from lumbar disc herniation grouped them into three sets. The first consisted of 20 individuals aged 58.4 ± 10.76 years, undergoing cosmogamma Cyborg laser treatment denoted as a gallium-aluminum-arsenide laser (GaAlAs laser) to provide a fiber output of at least 10W (± 10%). The second group included 25 patients aged 61 ± 10.47 years treated with Chattanooga ultrasound with 3 MHz for six minutes for the lumbar and paravertebral area. The third group had 20 individuals aged 54.6 ± 14.89 years named as a control group, which was maintained with a medical treatment plus modified pelvic tilt and straightening exercises with a follow-up of three months. After the follow-up, the group of patients with laser obtained a VAS score of 3.25, the ultrasound group 2.96, and the control 4.80, evidencing the benefit in pain tolerance (p=0.013) which can generate an improvement in mood, quality of life, and mental health (p=0.020).24

In comparison with our results, Williams exercises offer a great possibility of recovery and pain relief. However, when electrical stimulation was applied in a similar group, we found the patients perceived a decrease in pain yielding VAS values of 5.91 at five treatment sessions, culminating with 1.09 points at fifteen sessions (p≤0.05). These findings in the perceived reduction of pain by patients are similar to the use of electrical stimulation cited by other authors, where the time of use at the same frequency was similar, denoting the improvement referred to by the treatment. However, given that this area is still unknown to some sectors of the population, the use of these technologies are not always accepted by all affected patients.

There are several physiotherapeutic methods used for the relief of pain administered in combination with pharmacological products or their derivatives trying to control various musculoskeletal disorders, among which those related to the lumbar spine stand out. In addition to this, it is a priority to review the duration of the exercises for the improvement of pain and the consistent time for the evaluation, given that this is a substantial point to obtain exact information necessary for a recovery. If the exercises are performed incorrectly we may not reach the fundamental objective.25
Conclusion

The use of electrical stimulation therapy of interferential currents in analgesic modality in patients with lumbar disc herniation can offer improvement in the musculoskeletal quality of the individual, as well as their tolerance to pain. It should be mentioned that it must be used under specific standards and certain clinical specifications. It offers a range of possibilities for the rehabilitation of the condition, including complete improvement, and can help avoid lumbar surgery which, aside from entailing a painful recovery, is lengthy, and incurs a great cost to the health sector, to the patients, and to their families. However, re-education and prevention continue to be the primary means for care and reinforcement to avoid a relapse of these conditions.

Conflicts of interest
We declare that this research has no conflicts of interest.

Funding
No funding was received for the realization of this work.
Clinical and electroencephalographic study of infants with risk factors for neurological damage

Estudio clínico y electroencefalográfico en lactantes con factores de riesgo de daño neurológico

Abstract

Introduction: It’s estimated that between 3-5% of living newborns have neurology risk. The damage that occurs in perinatal period cause 55-75% of neurology deficit. Timely detection, follow-up and intervention permits prevent and/or minimize those aftermaths.

Objectives: To characterizer clinic and electroencephalographic of a group of children with neurology damage risk factors.

Methods: An early clinic-neurophysiologic evaluation of 87 infants in ages from one month to one year (M 67.53, SD 48.67 days, respectively) was carried out because they showed some neurology damage risk factor. They were undergoing to digital electroencephalography studies. The statistical analysis of data was performed with the Mann-Whitney U test, IC 95% in hypothesis test (p < 0.05).

Results: Birth risk factors had the highest frequency predominantly perinatal asphyxia and respiratory distress. The concurrence of 3 or more risk factors was discovered in 66.66% (58/87) of them. A percentage of 59.09 of EEG performed showed moderate disorders. There was a significant statistical association between clinical course of children and presence of seizures, as well as between gestational age, seizures and 3 or more risk factors.

Conclusions: The early clinical-electroencephalographic evaluation could be used to guide, modify or suggest therapeutic strategies and follow-up in infants with neurology damage risk factors.
Resumen

Introducción: Entre 3-5 % de los recién nacidos vivos tienen riesgo de daño neurológico. Los daños que ocurren en el período perinatal causan entre 55-75 % de los déficits neurológicos. La detección, seguimiento e intervención oportuna permite prevenir o minimizar estas secuelas.

Objetivos: Caracterizar clínica y electroencefalográficamente un grupo de niños desde 1 mes hasta el año de edad, con factores de riesgo de daño neurológico.

Métodos: Se realizó evaluación clínica y electroencefalográfica de 87 niños (media edad 67.53 días, desviación estándar 48.67) con algún factor de riesgo de daño neurológico, realizándoseles estudio electroencefalográfico digital. Para el análisis estadístico se utilizó el test no paramétrico U Mann-Whitney con un 95 % de confianza en las pruebas de hipótesis (p<.05)

Resultados: Los factores de riesgo natales fueron los más frecuentes predominando la asfixia perinatal y el distrés respiratorio. El 66.66 % (58/87) de los niños presentaron 3 o más factores de riesgo. De los EEG realizados, el 59.09 % mostraron alteraciones moderadas. Existió una asociación estadísticamente significativa entre la evolución clínica y la presencia de convulsiones, así como entre la edad gestacional y la presencia de convulsiones y 3 o más factores de riesgo.

Conclusiones: La evaluación clínica y electroencefalográfica temprana podría ser de utilidad para orientar, modificar o sugerir conductas terapéuticas y de seguimiento en recién nacidos con factores de riesgo de daño neurológico.

Palabras clave
Electroencefalograma, lactantes, factores de riesgo, daño neurológico.

Corresponding author:
Dr. Jorge Francisco Bosch-Bayard
Institute of Neurobiology
Unidad de Investigaciones en Neurodesarrollo, Universidad Autónoma de México
Boulevard Juriquilla 3001, Queretaro. CP: 76230
Tel.: 442 192 6101 ext. 117
E-mail: oldgandalf@gmail.com
Introduction

Infant brain damage is estimated at 2-5% of live births, with a series of prenatal, perinatal, postnatal, and social risk factors that increase the risk of developing neurodevelopmental deviations in children.

The damages that occur in the perinatal period cause 55-75% of the neurological deficits. Preterm newborns constitute a vulnerable population with a high risk of suffering medical problems and neurobehavioral disabilities including poor cognitive performance, greater learning difficulties, and an elevated risk of presenting behavioral disorders. Up to 47% of the total number of premature children present cerebral palsy, 27% show important cognitive disorders, and 23-37% sensory disorders.

Undetected neurodevelopmental deviations (NDD) that don't receive early intervention can cause children to face serious difficulties achieving an adequate level of education as well as full integration and social inclusion. Detection, follow-up, and timely intervention allow preventing and/or minimizing these negative consequences.

The electroencephalogram (EEG) has been one of the most widely used tools in the evaluation of premature babies, newborns with low birth weight, with asphyxia at birth, and neonatal seizures, among other risk factors for future development of NDDs.

The electroencephalogram (EEG) has been one of the most widely used tools in the evaluation of premature babies, newborns with low birth weight, with asphyxia at birth, and neonatal seizures, among other risk factors for future development of NDDs.

The EEG was performed in a room with dim light and in spontaneous sleep. The digital electroencephalograph MEDICID 5 (Neuronic SA) was used with an amplifier gain of 10,000, sampling frequency of 200 Hz, and filters with a bandwidth of 0.5-30 Hz. We used 19 surface electrodes placed according to the international system 10-20. Short-circuited electrodes located in both earlobes were used as reference. The visual inspection of the EEG was carried out offline by three experts independently.

Methods

This is a descriptive study of 87 patients from one month of birth to one year of age (mean 67.53 days, SD 48.67) referred to the Neurodevelopment clinic due to the presence of some neurological risk factor. A neurological risk factor is classified in children who, due to their pre-, peri-, or postnatal antecedents, are more likely to develop cognitive, motor, sensory, or behavioral problems in the first years of life, which may be transient or definitive. The data was obtained from the clinical records. Seventy-seven children received an EEG evaluation, and ten children were excluded because their parents did not give informed consent.

The EEG was performed in a room with dim light and in spontaneous sleep. The digital electroencephalograph MEDICID 5 (Neuronic SA) was used with an amplifier gain of 10,000, sampling frequency of 200 Hz, and filters with a bandwidth of 0.5-30 Hz. We used 19 surface electrodes placed according to the international system 10-20. Short-circuited electrodes located in both earlobes were used as reference. The visual inspection of the EEG was carried out offline by three experts independently.
The EEG studies were classified as: 

a) Normal, if the EEG activity was in accordance with their conceptional age at the time of the study;

b) With minimal alterations (immaturity of the base rhythms, interhemispheric asynchrony, voltage drop);

c) With moderate alterations (persistent focal or generalized acute spikes and waves);

d) With critical tracing (with focal patterns during crises, focal or multifocal monorhythmic discharges during crises);

e) With serious alterations (presence of isoelectric tracing or with a salvage suppression pattern).\(^{10}\)

The conceptional age is calculated as the sum of the baby’s gestational age in weeks at the time of birth, added to the chronological age of the baby in weeks at the time of the study.

In order to determine significant differences between the means of two populations, a statistical analysis was performed based on a non-parametric U Mann-Whitney test with a 95% confidence in the hypothesis tests (p<.05). The populations were formed considering the different risk factors in the sample studied. The results of the EEG and the clinical evolution of the 77 patients who underwent EEG were compared.

**Ethical Considerations**

An informed consent from the parents was requested to admit children to this study. Individual data were not disclosed and the established ethical norms were complied with. The research was approved by the Research Ethics Committee of the Juan Manuel Márquez Pediatric Hospital and the Faculty of Medicine of the Autonomous University of Querétaro, complying with the ethical standards of the Declaration of Helsinki of 2000.

**Results**

A total of 87 subjects were studied clinically. Neurological alterations predominated in the male sex (56.32% male and 43.68% female), of which 54 were full-term newborns and 33 pre-terms with an average gestational age of 36.84 weeks (SD 3.59, confidence interval: 25-42 weeks). The average birth weight was 2771 g (DE 915.58, confidence interval: 772-4506). In only 10 cases (30.30%) the weight was less than 1500 g.

When analyzing the behavior of the risk factors, Table 1 shows that the perinatal risk factors are the most frequent, with asphyxia and respiratory distress predominating. However, 66.66% (58/87) of the children showed the concurrence of three or more risk factors, 16.09% (14/87) presented two risk factors, and 17.24% (15/87) only one risk factor.

Neonatal seizures occurred in isolation (as the only risk factor) in 27.2%, associated with another risk factor in 18.1%, and with more than two risk factors in 53.7%.

Table 2 shows the results of the statistical analysis to determine significant differences between the populations with different risk factors in the sample studied.

The results of the clinical evaluation at one year of age showed that 70.02% presented a good clinical evolution (Table 3).

**EEG Results**

Of the total sample, 77 children received EEGs, the results of which are shown in Table 4. Note that 55.26% of the EEGs performed showed moderate alterations due to the presence of generalized or focal spikes and waves, persistent during tracing. The evaluation of the clinical manifestations and the EEG findings are shown in Table 5, showing no significant association between them.

In the study, 22 patients presented with neonatal seizures of which 81.82% (18/22) were full-term...
newborns. Of the total number of patients with neonatal seizures, the EEG tracing was normal in 13.63% (3/22), 9.09% (2/22) presented minimal alterations, 59.09% (13/22) moderate alterations, and 18.18% (4/22) serious alterations.

<table>
<thead>
<tr>
<th>Table 1. Distribution of Risk Factors.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factor</td>
</tr>
<tr>
<td>---------------------------------------</td>
</tr>
<tr>
<td><strong>Prenatal</strong></td>
</tr>
<tr>
<td>Vaginal infection</td>
</tr>
<tr>
<td>Threatened abortion</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Systemic arterial hypertension</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td><strong>Perinatal</strong></td>
</tr>
<tr>
<td>Prematurity</td>
</tr>
<tr>
<td>Low weight</td>
</tr>
<tr>
<td>Low Apgar</td>
</tr>
<tr>
<td>Perinatal asphyxia</td>
</tr>
<tr>
<td>Respiratory distress</td>
</tr>
<tr>
<td><strong>Post-natal</strong></td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Hydrocephalus</td>
</tr>
<tr>
<td>Hemorrhages</td>
</tr>
<tr>
<td>Social risk</td>
</tr>
<tr>
<td>95% confidence (p &lt;.05)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tabla 2. Results of the statistical analysis of the associated conditions.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated conditions</td>
</tr>
<tr>
<td>Gestational age - Seizures</td>
</tr>
<tr>
<td>Gestational age - Presence of 3 or more risk factors</td>
</tr>
<tr>
<td>Gestational age-Low birth weight</td>
</tr>
<tr>
<td>Gestational age - Perinatal asphyxia</td>
</tr>
<tr>
<td>Gestational Age - Respiratory distress</td>
</tr>
<tr>
<td>Presence of 3 or more risk factors - Low birth weight</td>
</tr>
<tr>
<td>Presence of 3 or more risk factors - Respiratory distress</td>
</tr>
<tr>
<td>Presence of 3 or more risk factors - Asphyxia at birth</td>
</tr>
<tr>
<td>Low weight - Respiratory distress</td>
</tr>
<tr>
<td>Low weight - Perinatal asphyxia</td>
</tr>
<tr>
<td>Low weight - Presence of 3 or more risk factors</td>
</tr>
<tr>
<td>Clinical evolution - Seizures</td>
</tr>
<tr>
<td>Perinatal asphyxia - Respiratory distress</td>
</tr>
<tr>
<td>95% confidence (p &lt;.05)</td>
</tr>
</tbody>
</table>
Table 3. Clinical evolution at one year of age of the subjects in the sample.

<table>
<thead>
<tr>
<th>Clinical evolution</th>
<th>% / N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good evolution</td>
<td>70.2 % (61/87)</td>
</tr>
<tr>
<td>PDR</td>
<td>9.3 % (8/87)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>12.6 % (11/87)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>2.3 % (2/87)</td>
</tr>
<tr>
<td>PDR and epilepsy</td>
<td>1.1 % (1/87)</td>
</tr>
<tr>
<td>Hydrocephalus and epilepsy</td>
<td>1.1 % (1/87)</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>1.1 % (1/87)</td>
</tr>
<tr>
<td>Cerebral palsy and epilepsy</td>
<td>2.3 % (2/87)</td>
</tr>
<tr>
<td>Total</td>
<td>100 %</td>
</tr>
</tbody>
</table>

PDR: Psychomotor Development Retardation.

Table 4. Electroencephalographic alterations of the sample.

<table>
<thead>
<tr>
<th>EEG</th>
<th>% / N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal EEG</td>
<td>18.42 % (14/77)</td>
</tr>
<tr>
<td>Minimal alterations</td>
<td>18.42 % (14/77)</td>
</tr>
<tr>
<td>Moderate alterations</td>
<td>55.26 % (43/77)</td>
</tr>
<tr>
<td>Critical tracings</td>
<td>0 %</td>
</tr>
<tr>
<td>Serious alterations</td>
<td>7.89 % (6/77)</td>
</tr>
</tbody>
</table>

Table 5. Association between clinical variables and the EEG.

<table>
<thead>
<tr>
<th>Associations</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG - Gestational age</td>
<td>0.68</td>
</tr>
<tr>
<td>EEG - Seizures</td>
<td>0.56</td>
</tr>
<tr>
<td>EEG - Low birth weight</td>
<td>0.92</td>
</tr>
<tr>
<td>EEG - Respiratory distress</td>
<td>0.60</td>
</tr>
<tr>
<td>EEG - Asphyxia</td>
<td>0.60</td>
</tr>
</tbody>
</table>

95% confidence (p <.05)

Discussion

The care provided to newborns in the neonatal intensive care unit (NICU) has led to their increased survival, but at the same time, an increasing number of high-risk newborns are discharged. These advances in neonatal critical care have improved survival rates, but have not managed to fully monitor the appearance of a series of neurodevelopmental sequelae in a significantly elevated portion of survivors. Sequelae include cerebral palsy, mental retardation, epilepsy, auditory and visual deficits, attention deficits, hyperactivity, and emotional lability, with later learning failures. The rate of severe neurological alterations in preterm infants weighing less than 1500 grams has remained between 10% and 30%, with less favorable results for those infants who are severely asphyxiated.

Perinatal asphyxia was the most representative risk factor in this study, coinciding with reports in the literature. Perinatal asphyxia is a serious incident in neonates due to hypoxia and generalized ischemia that causes biochemical and functional changes.
of a systemic nature, particularly in the central nervous system. Nagdyman et al. affirm that approximately a third of newborns with asphyxia present hypoxic-ischemic encephalopathy. The diagnosis of a perinatal asphyxia event implies the early onset of a neonatal neurological syndrome. Several studies have proven the neurological sequelae of perinatal hypoxia, which can range from mild to severe.

Neonates with perinatal asphyxia who are more at risk of dying or have subsequent neurological disability are those who have persistent low Apgar scores, other neurological signs, and seizures in the first 48 hours of life. The score of the Apgar at five minutes of life is the one that presents greater concordance with the metabolic acidosis and better correlation with the risk of neurological sequelae, although the presence of a normal Apgar score does not exclude the possibility of future neurological sequelae. A study by González de Dios reports that 47.1% of newborns with tachypnea in their sample presented extraneurological manifestations, the most frequent being respiratory pathology, mainly respiratory tachypnea of the newborn, and meconial fluid aspiration syndrome. This research corroborated a strong statistical association between respiratory distress and perinatal asphyxia.

Seizures in the neonatal period are the main clinical expression of CNS dysfunction. Unlike in other pediatric ages, in this period they are idiopathic only exceptionally (1-2%). It is considered that 0.15 to 1.4% of newborns present seizures in this stage, reaching up to 6% in newborns under 36 weeks. The incidence increases until reaching 25% if the population of neonates of NICU is analyzed, which coincides with what was reported in this investigation.

Neonatal seizures can be occasional due to an acute neuronal dysfunction as a result of a brain attack, or they can be repeated chronically configuring epilepsy. In the first case, 10-30% will evolve into secondary epilepsy in the infant or the older child, and in the second, some will progress to epilepsy in later stages or will self-limit to the neonatal period.

In this investigation, an association between gestational age and neonatal seizures becomes evident. A study by Sheth et al. analyzing the relationship between these two conditions found a parabolic distribution with a lower incidence between 30 and 36 weeks (4.8%) compared to the term group (11.9%), while in extremely premature infants with less than 30 weeks of gestation the incidence was 14.1%. The results of this study coincide with that reported by other authors. Most of the patients who presented seizures were full-term (81.82%) compared to 18.18% preterm newborns. This behavior has been related to the underlying etiology: intraventricular hemorrhage in extremely premature infants and hypoxic-ischemic encephalopathy in full-term infants. Hypoxic-Ischemic Encephalopathy (HIE) is a neurological syndrome caused by failure in the supply of oxygen and cerebral perfusion and occurs in one to three of every 1000 live full-term infants. Neonates with moderate encephalopathy have a relatively low mortality (5%) and neurological sequelae present in 20-40% of survivors. Those who have a severe HIE have a 75% chance of dying (75%), while 60-100% of survivors have severe neurological sequelae.

The EEG alterations described in the group of patients who presented neonatal seizures in this investigation are similar to those found by Campistol et al. highlighting that most of the patients presented moderate and severe alterations. Alcover-Blocha et al. report that the recording of a pathological EEG (critical or with serious alterations) is associated with an unfavorable evolution in most cases. A more accurate prognosis in these patients can be made from the etiology of neonatal seizures and EEG patterns. The persistence of pathological records beyond 72 hours of birth is invariably associated with death or serious neurological sequelae, while early recovery, before 12 or at least 36 hours, is associated with normal results or with minor neurological alterations. In general, existing research studies on electroencephalography in infants at high risk of neurological damage are
scarce, with small samples, addressing different views of the problem, and without strict monitoring during the neonatal period.

In the study by Jiménez et al. the appearance of clinical neurological alterations during the first week of life, such as the presence of seizures and a pathological EEG, are described as the main prognostic factors in perinatal asphyxia. Similar conclusions were obtained by Andre et al. who stated that those asphyctic newborns who continued to present clinical and EEG alterations on the seventh day of birth, later showed sequelae in up to 75% of the cases.

Conventional electroencephalography has a series of limitations in the study of these patients, among which are: difficulties in prolonged monitoring, excessive number of electrodes, electrical interference by environmental equipment, difficulties in the interpretation of the study (when staff with training in clinical neurophysiology is necessary), and the realization of such brief registers (45-60 minutes) that, even with periodic evaluations, information is lost on the evolution of the alterations of the base activity, sleep states, and sporadic convulsions. The incorporation of EEG integrated by amplitude (EEGa), also known as brain function monitor, is a simple method of continuous recording of cortical electrical activity which allows predicting the final neurological evolution in as short a time as the first six hours of life.

Neurological lesions in newborns may have an onset in the prenatal stage and can be explained by the activation of inflammatory cascades that seem to predominate more in male neonates, as in our sample. This coincides with the results of other authors, so it is assumed the possible existence of neuroprotective factors for the female gender.

Three-quarters of our sample had an overlap of risk factors. A study conducted by Salinas-Álvarez et al. in patients with a high neurological risk described that on a scale of 1 to 10 risk factors, their sample had an average of 4.1 factors. It has been reported that these cases are more likely to develop some disability and that the accumulation of risks is not equivalent to a sum but rather that its effect is enhanced. Some risk factors carry a higher risk of causing an impairment of psycho-neuro-sensorial development, among which weight at birth stands out.

On the other hand, the prediction of morbid damage has made necessary the search of biochemical, neurophysiological, and neuroimaging indicators by morphological and functional alterations to identify early lesions that threaten the satisfactory evolution of children.

Bearing in mind that the interval between the initial neurological injury and the development of permanent damage offers a window of opportunity to start therapeutic interventions to stop the damage or promote neurological evolution, it is crucial to identify high-risk newborns who may benefit from neuroprotective management.
Conclusions

Early clinical and electroencephalographic evaluation could be useful in guiding, modifying, or suggesting therapeutic and follow-up options for newborns with risk factors of neurological damage. It would be crucial to create programs that allow early evaluation and follow-up of newborns identified with risk factors.

Conflicto de intereses
The authors declare that in this study there are no relevant conflicts of interest.

Fuentes de financiamiento
There was no particular source of funding for this scientific report because the patients come from the free public health service.
References


Original contribution

Alejandra Mancilla-Ramírez,1 Gloria Araceli García-Miranda.2

1Medical Specialist in Rehabilitation Medicine. High Specialty Course in Pediatric Rehabilitation. Deputy Medical Director of the Teleton Child Rehabilitation and Inclusion Center Clinic, State of Mexico.
2Professor-Researcher at the School of Medicine of the University of Iztacala, UNAM.

Frequency of Pediatric Spinal Cord Injury. 9 years experience

Abstract

Introduction: The World Health Organization defines spinal cord injury (SCI) as damage suffered in the spinal cord as a result of trauma: like a car accident, a disease or spinal cord degeneration, as in cancer. There are no reliable estimates of global prevalence; it is estimated that its annual incidence ranges from 40 to 80 cases per million inhabitants. Up to 90% of these cases are due to traumatic causes, although the proportion of non-traumatic SCI seems to be increasing. The SCI in children and young people is rare; however, it generates a significant physical and psychologically impact in the child.

Objective: To establish the frequency and etiology of spinal cord injury in children and adolescents in the CRIT State of Mexico.

Methods: This is a descriptive study of prevalences in which all the records of patients with a medical history of spinal cord injury were reviewed in the Centro de Rehabilitación e Inclusión Infantil Teléton Estado de México in the last 9 years. The data included were age, gender, cause of spinal cord injury, topography and neurological level according to the classification of the American Spinal Cord Injury Association (ASIA).

Results: In the spinal cord injury clinic from September 2008 to November 2017, 47 patients with a diagnosis of SCI Were admitted, with age ranging from 9 months to 19 years. 27 male/20 female were included. The most frequent cause of SCI were nontraumatic causes in 31 (65.9%) cases, being the tumoral etiology the most representative cause. Traumatic causes were presented in 16 (34%) patients. Of the 47 cases reviewed, due to their clinical presentation, 26 (55.3%) were incomplete and 21 (44.6%) complete.

Conclusions: The etiology of spinal cord injury was non-traumatic in children under 10 years, the most frequent type being complete spinal cord injury.

Keywords
Spinal cord injury, spinal trauma, pediatric rehabilitation.
Resumen

Introducción: La Organización Mundial de la Salud define a la Lesión Medular (LM) como los daños sufridos en la médula espinal: a consecuencia de un traumatismo (accidente automovilístico), una enfermedad o la degeneración de la médula como en el caso del cáncer, no existen estimaciones confiables de la prevalencia mundial; se calcula que su incidencia anual oscila entre 40 y 80 casos por millón de habitantes. Hasta un 90% de esos casos se debe a causas traumáticas, aunque la proporción de LM de origen no traumático parece ir en aumento. La LM en los niños y jóvenes es poco frecuente, sin embargo, genera un impacto significativo a nivel físico y psicológico tanto en el niño, como en su familia y entorno.

Objetivo: Establecer la frecuencia y etiología de la lesión medular en niños y adolescentes en el Centro de Rehabilitación e Inclusión Infantil Teletón Estado de México.

Métodos: Es un estudio descriptivo de prevalencias en el que se revisaron todos los expedientes de pacientes con historia clínica de lesión medular en los últimos 9 nueve años. Los datos incluidos fueron: edad, género, causa de la lesión medular, topografía y nivel neurológico de acuerdo con la clasificación de la American Spinal Cord Injury Association (ASIA de sus siglas en inglés).

Resultados: En la clínica de lesión medular de septiembre de 2008 a noviembre de 2017, ingresaron 47 pacientes con diagnóstico de LM, con un rango de edad entre 9 meses y 19 años. Se incluyeron 27 masculinos y 20 femeninos. Las causas más frecuentes de LM fueron las no traumáticas, presentadas en 31 casos (65.9%) siendo el origen tumoral la causa más representativa, las causas traumáticas se presentaron en 16 pacientes (34%). Los 47 casos analizados, por su presentación clínica fueron 26 (55.3%) LM incompleta y 21 (44.6%) LM completa.

Conclusiones: La etiología de lesión medular fue la no traumática en menores de 10 años, con mayor frecuencia la lesión medular incompleta.

Palabras clave
Lesión medular, trauma medular, rehabilitación pediátrica.

Correspondencia:
Alejandra Mancilla Ramírez.
Medical Specialist in Rehabilitation Medicine. High Specialty Course in Pediatric Rehabilitation. Deputy Medical Director of the Teleton Child Rehabilitation and Inclusion Center Clinic, State of Mexico.
Avenida Gustavo Baz No. 219, Colonia San Pedro Barrientos, Tlalnepantla de Baz, Estado de México CP 54010
Tel: 53212223 Ext. 2155
E-mail mancilla@teleton.org.mx
Introduction

The World Health Organization (WHO) defines spinal cord injury (SCI) as damage to the spinal cord as a result of trauma (such as a motor vehicle accident), a disease (like transverse myelitis), or degeneration of the spinal cord (as with cancer). There are no reliable estimates of global prevalence, but it is estimated that its annual incidence ranges between 40 and 80 cases per million inhabitants. Up to 90% of these cases are due to traumatic causes, although the proportion of non-traumatic origin SCI appears to be increasing. Though the exact frequency of SCI is unknown, between 250,000 and 500,000 people worldwide suffer from SCIs every year according to a WHO report from 2013. It is possible that the actual incidence is higher due to unreported cases of death at the scene of the accident or during transportation to the hospital. The WHO reports that, in the United States, SCIs in children under 15 represent less than 4% of the annual incidence of all cases of acquired SCIs. This figure is similar to what Romero and Ramírez report regarding the fact that SCIs in children are relatively rare since they represent between 2 and 5% of all spinal injuries.

In men, the risk of SCI is higher in young adults between the ages of 20 and 29 and in the elderly after the age of 70. In women, on the other hand, the greatest risk is registered in adolescence between the ages of 15 and 19 and after the age of 60. The male-female ratio is at least 2:1, although in some cases it can be higher.

Most SCIs are due to preventable causes such as traffic accidents, falls, or acts of violence. People with SCIs are two to five times more likely to die prematurely than those without. The lowest survival rates are in low- and middle-income countries. SCIs are associated with lower rates of schooling and economic participation.

Spinal cord injuries are rare in children and young people, but they have a significant physical and psychological impact on them as well as on their family and environment. SCIs represent an important cost to those who suffer from them and to society as a whole.

Anatomical and physiological differences in children and adolescents, together with growth and development, are responsible for the manifestations and complications of SCI in the pediatric patient.

This is because the pediatric cervical spine is hypermobile, due to ligament laxity and horizontalization of the facets. In children, Spinal Cord Injury Without Radiographic Abnormalities (SCIWORA) have been found more frequently, conditioned by the relative hypermobility of the spine. These peculiarities are due to the different biomechanical behavior of children, especially those under 10 years of age.

Pediatric SCI is a little-studied nosological entity, probably due to the scarce information reported worldwide and the little knowledge of its etiology; however, it is one of the reasons for care in child rehabilitation services that requires comprehensive management due to its sequelae and complications.

Materials and methods

This is a descriptive study of prevalence. All patient files with a clinical history of spinal cord injury at the Center for Child Rehabilitation and Inclusion of the State of Mexico in the last nine years were reviewed. Data included were age, gender, cause of spinal cord injury, topography, and neurological level according to the classification of the American Spinal Cord Injury Association (ASIA).
Results

Forty-seven patients with a diagnosis of SCI were admitted at the spinal cord injury clinic from September 2008 to November 2017. They ranged in age from 9 months to 19 years, with an average age of 4 years (Figure 1).

Of the 47 patients analyzed, 23 men and 16 women were included, a ratio of 1.4:1 (Figure 2).

The most frequent causes of SCI were non-traumatic in 31 cases (65.9%). Tumor origin was the most representative cause in 11 patients with a diagnosis of retroperitoneal neuroblastoma, medullary pilocytic astrocytoma. Five cases presented with an infectious origin (transverse myelitis), four cases with neonatal hypoxia, and the last five had multiple vascular origins: arteriovenous malformations (AVM), aortic aneurysms, extradural hematoma and medullary ischemia due to cardiac malformation at birth and coarctation of the aorta (Table 1).

Sixteen patients presented with traumatic causes (34%). Six cases were vertebral fractures secondary to car accidents, five cases of accidents due to falls from heights, three cases of gunshot wound, one was run over by a car, and one obstetric trauma (Table 2).

Of the 47 cases analyzed, 26 were incomplete SCI (55.3%) and 21 were cataloged as complete SCI (44.6%) due to their clinical presentation (Figure 3).

The topographic presentation was in the following distribution: 15 cases of flaccid paraplegia (31.9%), nine of spastic paraparesis (19.1%), eight of spastic paraplegia (17%), five of spastic quadriplegia (10.6%), four of flaccid paraparesis (8.5%), three mixed quadriplegia (6.3%), one double hemiparesis (2.1%), one spastic diparesis (2.1%), and one mixed paraplegia (2.1%) (Table 3).

According to the ASIA classification, 21 patients were classified as type A (44.6%), 13 as type C (27.6%), nine as type B (19.1%), and four as type D (8.5%) (Figure 4).

Discussion

Spinal cord injury in the pediatric and adolescent population is a rare pathological entity in the Mexican population attending CRIT in the State of Mexico. Other origins of motor disability such as cerebral palsy, neuromuscular diseases, or birth defects such as neural tube defects affecting the spine, specifically myelomeningocele, are the main reasons for care.

The population studied in the last nine years with spinal cord alterations was 251 patients, of which only 47 had a diagnosis of SCI (18.7%).

The literature mentioning frequent traumatic causes of SCI include Hagen<sup>4</sup> and Wang<sup>5</sup>, reporting that they’re associated with car and pedestrian accidents in children and with car and motorcycle accidents in adolescents. Posadas reports 14 cases of child spinal cord trauma of which 50% were caused by traffic accidents and 33.3% by falls from a height in their home. Gunshot wounds and mistreatment were rare.<sup>10</sup>

Costacurta reports that 50.9% had traumatic origin (gunshot 42.6%, run over by a car 9.3%, direct trauma 5.6%), non-traumatic origin 49.1%, tumors 36.5%, infections 19.2%, vascular disease 15.9%, spinal malformations 11.5%, syringomyelia 3.8%, and non-established etiology 13.5%.<sup>3</sup>

Claret reports in four cases (25%) the cause of SCI was obstetric trauma, in seven of the cases (43.7%) the cause was traumatic: three motorcycle accidents, two traffic accidents, one was run over by a car, and another was a fall. The malformation cause includes two patients (12.5%) affected by a medullary arteriovenous malformation. In three patients (18.7%) the lesion appeared in the immediate postoperative period of spine surgery (one cervical and two dorsal).<sup>7</sup>

Our results differ from those of the authors mentioned since we found that 31 cases of the studied population (65.9%) presented a non-traumatic origin as a cause of the SCI and only...
16 patients had trauma as etiology (34%). The inversion of the etiology is probably the result of better prevention of accidents and the specific diagnosis of the diverse nosological entities causing spinal cord damage. This study did not include neural tube defects of vertebral location (myelomeningocele) as part of the etiologies.

Regarding the age of presentation in our research, children under 10 years (59.5%) were the most affected, similar to what is described in the literature. Claret in 2006 reports that out of 16 patients included in the study, 12 were male, with ages between a few hours of life and 19 years eight months, with an average of 10 years. Costacurta et al. on the other hand, conducted a study at the Association of Assistance for Child Disability based in Sao Paulo, Brazil, from April 2002 to June 2008 analyzing 1953 cases of patients, children from 0 to 16 years, 106 patients over 16 years. The frequency of SCI was 5.4%, 63.2% were males, with an average age in males of 8.6 years (mean 9 years). The presentation by gender in our study was predominantly men, similar to what the WHO and Parente mentioned in 2005: out of 86 children who suffered spinal trauma 45 were boys and 41 girls, which represents a ratio of 1.1:1.6

In relation to neurological involvement, 55% of cases result in tetraplegia and 45% in paraplegia below the first thoracic level. Claret also mentions that the most common level was paraplegia with 76.4%. Coinciding with the results of this study, 51% presented paraplegia, contrasting with the fact that there were no cases of quadriplegia, but quadriparesis in 17% of the population.
**Table 1.** Pediatric Spinal Cord Injury Frequency by Non-Traumatic Etiology  

<table>
<thead>
<tr>
<th>Non-Traumatic Cause</th>
<th>No. Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor (Retroperitoneal Neuroblastoma)</td>
<td>11 (35.4%)</td>
</tr>
<tr>
<td>Infectious (Transverse Myelitis, Amebiasis)</td>
<td>5 (16.1%)</td>
</tr>
<tr>
<td>Vascular (AVM, aneurysms, hematomas, ischemia)</td>
<td>5 (16.1%)</td>
</tr>
<tr>
<td>Neonatal Hypoxia</td>
<td>4 (12.9%)</td>
</tr>
<tr>
<td>Metastases from Lymphoblastic Leukemia</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>Post-chemotherapy for Lymphoblastic Leukemia</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>Narrow Cervical Canal Syndrome in Achondroplasia</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>CNS malformation (Arnold Chiari Syndrome 1)</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>CNS Demyelinating Disease (De Devic)</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>Spine Surgery for Scoliosis</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>31 (100%)</td>
</tr>
</tbody>
</table>

**Table 2.** Pediatric Spinal Cord Injury Frequency by Traumatic Etiology.  

<table>
<thead>
<tr>
<th>Traumatic Cause</th>
<th>No. Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Car accident</td>
<td>6 (37.5%)</td>
</tr>
<tr>
<td>Falls from heights, stairs</td>
<td>5 (31.2%)</td>
</tr>
<tr>
<td>Gunshot</td>
<td>3 (18.7%)</td>
</tr>
<tr>
<td>Obstetric trauma</td>
<td>1 (6.2%)</td>
</tr>
<tr>
<td>Ran over by a car</td>
<td>1 (6.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>16 (100%)</td>
</tr>
</tbody>
</table>

**Figure 3.** Pediatric Spinal Cord Injury Frequency by Clinical Presentation.  

<table>
<thead>
<tr>
<th>Topography</th>
<th>No. Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flaccid Paraplegia</td>
<td>15 (31.9%)</td>
</tr>
<tr>
<td>Spastic Paraparesis</td>
<td>9 (19.1%)</td>
</tr>
<tr>
<td>Spastic Paraplegia</td>
<td>8 (17%)</td>
</tr>
<tr>
<td>Spastic Quadriparesis</td>
<td>5 (10.6%)</td>
</tr>
<tr>
<td>Flaccid Paraparesis</td>
<td>4 (8.5%)</td>
</tr>
<tr>
<td>Mixed Quadriparesis</td>
<td>3 (6.3%)</td>
</tr>
<tr>
<td>Double Spastic Hemiparesis</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>Spastic Diparesis</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>Mixed Paraplegia</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>47 (100%)</td>
</tr>
</tbody>
</table>

Conclusions

Spinal cord injury is rare in the pediatric age in the Mexican population that attends the CRIT, State of Mexico. The most frequent etiology in this study was nontraumatic, mainly of tumoral origin with a greater presentation in children under 10 years. Incomplete spinal cord injury was the most common at 53.8%. The most frequent topography was flaccid paraplegia, spastic paraplegia, and spastic paraparesis in 68%.

The highest percentage of cases (44.7%) was at level A of the ASIA classification.

It would be important to consider conducting a multi-center study to increase the population and obtain national figures that reflect the national behavior of this entity as a cause of motor disability in children under 18 years of age.

Conflicts of interest
We declare that this research has no conflicts of interest.

Funding
No funding was received for the realization of this work.
References

Anti-CGRP Monoclonal Antibodies for the Treatment of Chronic and Episodic Migraines

Anticuerpos monoclonales contra el CGRP para el tratamiento de la migraña crónica y episódica

Abstract

Migraine is a clinical condition that causes neurological disability in a high percentage of the economically active population. This disorder is characterized by pulsatile unilateral headache accompanied by other neurovascular phenomena. The disease can acquire a chronic behavior forcing patients to receive preventive treatment for a long time period. However, many drugs currently available for the chronic treatment cause different side effects that limit their use and most of them were not designed specifically for migraine prevention. Evidence of the role that calcitonin gene related peptide (CGRP) plays in the mechanisms of central sensitization and in the physiopathology of migraine has led to the development of therapies directed to limit its biological activity, among which there are four new monoclonal antibodies against that molecule or its receptor. Clinical trials carried out so far with these antibodies provide evidence in favor of their use in the treatment and control of migraine, therefore, in this review we discuss the results of such studies and provide the physiological and molecular bases that support the use of the CGRP as a therapeutic target.
Review

Monoclonal antibodies to treat migraines

Resumen

La migraña es una condición clínica que provoca discapacidad en un porcentaje alto de la población económicamente activa. Este padecimiento se caracteriza por una cefalea unilateral pulsátil acompañada de otros fenómenos neurovasculares. La enfermedad puede adquirir un comportamiento crónico que obliga al paciente a recibir un tratamiento preventivo por un largo periodo de tiempo. Sin embargo, muchos fármacos hoy disponibles para dicho propósito causan diferentes efectos adversos que limitan su uso y la mayoría de ellos no fueron diseñados específicamente para la prevención de la migraña. La evidencia de la participación del péptido relacionado con el gen de la calcitonina (CGRP) en los mecanismos de sensibilización central al dolor y en la fisiopatología de la migraña ha llevado al desarrollo de tratamientos dirigidos a limitar su actividad biológica, entre los que se encuentran cuatro nuevos anticuerpos monoclonales contra dicha molécula o su receptor. Los ensayos clínicos hasta ahora realizados con estos anticuerpos aportan evidencia a favor de su empleo en el tratamiento y control de la migraña, por lo que en esta revisión se discuten los resultados de dichos estudios y se proveen las bases fisiológicas y moleculares que sustentan el uso del CGRP como blanco terapéutico.

Palabras clave
Péptido relacionado con el gen de la calcitonina, migraña, anticuerpos monoclonales, cefalea.

Corresponding author:
Dr. Parméndes Guadarrama Ortiz.
Departamento de Neurocirugía, Centro Especializado en Neurocirugía y Neurociencias México, Tlaxcala & Manzanillo No. 94, Roma Sur 06760, Ciudad de México, México.
E-mail: investigacion.cientifica@cennm.com
Introducción

Migraine is one of the main causes of disability worldwide. It is estimated that 15% of the population under the age of 50 suffer from this neurological disorder, which has a higher prevalence in women than in men. It is characterized by the presence of a pulsatile unilateral headache of moderate to severe intensity, aggravated by movement, lasting 4 to 72 hours, accompanied by nausea or vomiting, phonophobia and photophobia. In most patients, headache occurs less than 15 days per month (episodic migraine); however, 2 to 3% of the subjects will develop a chronic form of the disease defined as the occurrence of 15 or more days with headache per month for more than three months, with at least eight of these pain attacks fulfilling the characteristics of a migraine, with or without aura, which can decrease with a triptan or ergotamine derivative, and for which there is no other alternative diagnosis within the definitions of the latest International Classification of Headaches, 3rd edition, recently published.

Chronic migraine causes a great impact on the quality of life of patients, affecting their work life and interpersonal relationships. Recurrent pain attacks require the initiation of prophylactic treatment with any of the drugs currently available for this purpose, which include anticonvulsants, tricyclic antidepressants, beta blockers, and calcium channel blockers. However, adherence to treatment is affected by the high incidence of adverse effects and drug interactions of these medications, of which none was developed specifically for the management of migraine. In fact, onabotulinum toxin A is the only drug approved by the FDA for the management of chronic migraine, although it does not dramatically reduce the number of days with headache. Therefore, there is an urgent need for drugs aimed at counteracting the underlying pathophysiological mechanisms of chronic migraine. Evidence generated for more than 30 years supports the participation of the calcitonin gene-related peptide (CGRP) in the functional alterations that lead to the central sensitization to pain in subjects with headache, supporting its use as a new therapeutic target. Recent efforts have been aimed at interrupting the activity of CGRP from different approaches, the most novel of which is the use of humanized monoclonal antibodies directed to neutralize the peptide or to block its receptor. The results of the clinical trials to date with these antibodies in patients with chronic and episodic migraine show positive results that could represent a new era in the management of this condition, although their safety and cost-benefit must be analyzed before displacing other therapeutic measures currently in use. Therefore, in this review, we provide a summary of the evidence derived from basic and clinical research that supports the use of anti-CGRP monoclonal antibodies for the preventive treatment of migraine.

Cgrp as a therapeutic target: physiopathological and molecular basis

Migraine is a disorder whose origin is still unknown. Although for a long time it was considered a vascular disorder, recent evidence suggests that there is a primary neurogenic cause with secondary vascular phenomena. What is clear is the involvement of the trigeminal nerve and the nucleus caudalis in the mechanisms of initiation and maintenance of pain sensitization underlying chronic migraine, probably through its activation by peripheral inflammatory mediators or by a dysfunction in the processing of afferent stimuli that could be misinterpreted as painful and accessing the central sensory areas through the trigeminovascular system.

The CGRP is a 37-amino acid neuropeptide involved in the central and peripheral events of migraine. It belongs to the calcitonin family along with amylin, adrenomedullin-2, and adrenomedullin. It is encoded by the same calcitonin gene through an alternative splicing mechanism of mRNA, which generates two isoforms of CGRP. Both isoforms are preferentially expressed in nerve tissue, especially in A delta and C fibers; the alpha isoform is present.
in the trigeminal nerve terminals and the beta isoform predominates in the enteric peripheral nervous system.\textsuperscript{19, 20} The two peptides exert their activity through their binding to their receptor, which is heterodimeric and is composed of three subunits: calcitonin receptor-like receptor (CLR, protein with 7-transmembrane domains), receptor activity-modifying protein (RAMP1), and receptor component protein (RCP).\textsuperscript{21} The CGRP is a potent vasodilator which made it a candidate to be an active mediator during migraine attacks.\textsuperscript{12, 16, 22} Currently, due to its different functions, it is believed that its participation is crucial to increase sensory activity at different levels since it is a neuromodulator that can potentiate glutamate-mediated synaptic transmission leading to central sensitization in trigeminal sensory terminals and other central nuclei.\textsuperscript{23-25} During spontaneous or induced migraine events, CGRP levels rise markedly and can be measured in different biological samples.\textsuperscript{16} Likewise, administration of the recombinant peptide induces migraine attacks in subjects with the disease and headache symptoms in healthy individuals.\textsuperscript{26, 27} Treatment with triptans drastically decreases CGRP concentrations and the measurement of this molecule has been proposed as a biomarker of the disease.\textsuperscript{28, 29} However, by far the most solid evidence supporting the participation of this peptide in the pathophysiological mechanisms of migraine was provided by clinical trials conducted with CGRP receptor antagonists called gepants, of which only the ubrogepant continues to be tested in clinical trials (NCT02828020) because the rest caused concerns about potential liver toxicity.\textsuperscript{30-35} In these studies, it was observed that the antagonism of the signaling mediated by the binding of CGRP to its receptor significantly decreased the frequency and duration of migraine attacks.

Based on clinical and molecular evidence, the current model suggests that some migraine-initiating stimuli induce an elevation of CGRP levels, increasing synaptic transmission and resulting in pain and altered sensory perception.\textsuperscript{17} However, this peptide could also contribute to the mechanisms of neurogenic inflammation, peripheral sensitization, aversion to light, cortical depression, and vasodilation that occur in migraine.\textsuperscript{36}

**Clinical trials with monoclonal antibodies targeting cgrp or its receptor**

To date, four humanized antibodies directed against CGRP have been developed with which clinical trials are being carried out. Of these four, Fremanezumab, Eptinezumab, and Galcanezumab bind specifically to the peptide, and Erenumab blocks the CGRP receptor.

A meta-analysis conducted in 2017 reported that, in general, antibodies against CGRP significantly reduce migraine days per month from baseline with an average of 1.6 days compared with the placebo group.\textsuperscript{37} Following this meta-analysis, four more advanced clinical trials have been published, the results of which are shown in Table 1. The most important characteristics of each antibody are summarized below as well as the studies that support its use in the preventive treatment of migraine.

**Fremanezumab**

Fremanezumab (TEV-48125) is a humanized monoclonal antibody isotype IgG2a that binds selectively to the alpha and beta isoforms of CGRP.\textsuperscript{38} Its low nonspecific reactivity against other molecules structurally related to CGRP diminishes its potential to induce toxicity. Pre-clinical studies demonstrated its efficacy in interfering with CGRP signaling through its receptor in vitro. The first in vivo tests in rats showed that Fremanezumab is capable of inhibiting the vasodilatation of the middle meningeal artery in response to electrical stimulation. Likewise, in non-human primates (NHP), this antibody counteracted the vasodilatory response induced by the administration of capsaicin in a dose-dependent manner.\textsuperscript{39} Its long half-life initially caused concern about the possible impact of chronic inhibition of CGRP on cardiovascular function. However, in a study conducted in NHP, no alterations in cardiovascular parameters were observed after chronic administration for 14 weeks and, in six phase I trials, the administration of Fremanezumab intravenously
Table 1. Results of the most recently published clinical trials on the use of anti-CGRP antibodies for the treatment of migraine.

<table>
<thead>
<tr>
<th>Antibody/ Clinical trial</th>
<th>Type of migraine</th>
<th>Treatment schedule</th>
<th>Reduction in the number of days with migraine</th>
<th>Reduction in the number of days of use of other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fremanezumab (TEV-48125)/ NCT02621931</td>
<td>Chronic</td>
<td>Placebo SC every 28 days for 3 months</td>
<td>2.5±0.3*</td>
<td>1.9±0.3*</td>
</tr>
<tr>
<td></td>
<td>Episodic</td>
<td>675 mg / placebo / placebo SC every 28 days for 3 months</td>
<td>4.3±0.3* (p&lt;0.001)</td>
<td>3.7±0.3* (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>Episodic</td>
<td>675mg/225mg/225mg SC every 28 days for 3 months</td>
<td>4.6±0.3* (p&lt;0.001)</td>
<td>4.2±0.3* (p&lt;0.001)</td>
</tr>
<tr>
<td>Galcanezumab (LY2951742)/ NCT02614183</td>
<td>Episodic</td>
<td>Placebo SC monthly for 6 months</td>
<td>2.8+</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Episodic</td>
<td>120 mg SC monthly for 6 months</td>
<td>4.7+ (p&lt;0.001)</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Episodic</td>
<td>240 mg SC monthly for 6 months</td>
<td>4.6+ (p&lt;0.001)</td>
<td>--</td>
</tr>
<tr>
<td>Eptinezumab (ALD403)/ NCT01772524</td>
<td>Episodic</td>
<td>Placebo IV single dose</td>
<td>4.6***</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Episodic</td>
<td>1000 mg IV single dose</td>
<td>5.6***</td>
<td>--</td>
</tr>
<tr>
<td>Erenumab (AMG 334)/ NCT02483585</td>
<td>Episodic</td>
<td>Placebo SC monthly for 3 months</td>
<td>1.8*</td>
<td>0.6*</td>
</tr>
<tr>
<td></td>
<td>Episodic</td>
<td>70 mg SC monthly for 3 months</td>
<td>2.9* (p&lt;0.001)</td>
<td>1.2* (p=0.002)</td>
</tr>
</tbody>
</table>

* Defined as the number of days in which headache lasted >4 hours, moderate to severe intensity, or required the use of triptans or ergotamine; the results of the treatments are shown to be significantly lower compared to placebo; the follow-up was until week 12 after the first application of the treatment.
** Efficacy during the first month of treatment.
*** Efficacy between week 5 and 8 of treatment.
+ Defined as the number of days in which headache with duration >30 min occurred with both of the following clinical conditions: A (at least two characteristics: unilateral, pulsatile, moderate to severe pain and aggravation with physical activity) and B (at least one: nausea and/or vomiting and/or photophobia and phonophobia). Follow-up during 6 months of treatment and up to 5 months after the last application.
IM: intramuscular, SC: subcutaneous, IV: intravenous, NS: not significant.
## Reduction in the score of functional scales

<table>
<thead>
<tr>
<th>Reduction in the score of functional scales</th>
<th>Frequency of adverse effects</th>
<th>Common adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5±0.5* (HIT-6 score)</td>
<td>64%</td>
<td>Pain, induration, erythema, or hemorrhage at the site of injection, upper respiratory tract infections, dizziness, nausea.</td>
</tr>
<tr>
<td>6.4±0.5* (p&lt;0.001) (HIT-6 score)</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>6.8±0.4* (p&lt;0.001) (HIT-6 score)</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>Ref (MSQ score)</td>
<td>60.4%</td>
<td>Infection of the upper respiratory tract, pain and reaction at the injection site, nasopharyngitis, nausea, pruritus.</td>
</tr>
<tr>
<td>7.7±1.3 (p&lt;0.001) (MSQ score)</td>
<td>65.5%</td>
<td></td>
</tr>
<tr>
<td>7.4±1.3 (p&lt;0.001) (MSQ score)</td>
<td>67.7%</td>
<td></td>
</tr>
<tr>
<td>--</td>
<td>52%</td>
<td>Infections of the upper respiratory tract, urinary infections, fatigue, back pain, nausea, vomiting, and arthralgia.</td>
</tr>
<tr>
<td>--</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>54.7%</td>
<td>Infections of the upper respiratory tract, pain at the injection site, nasopharyngitis. Development of non-neutralizing anti-Erenumab antibodies in 4.3% of subjects.</td>
</tr>
<tr>
<td>NS</td>
<td>48.1%</td>
<td></td>
</tr>
</tbody>
</table>
**Figure 1.** Participation of CGRP in the pathophysiology of chronic migraine and mechanism of action of monoclonal antibodies developed against said peptide. **A)** The CGRP is expressed in the trigeminal nerve terminals. **B)** In patients with migraine, the concentrations of this molecule increase during the attacks of pain, causing a dilating effect on the dural vessels and an exacerbation of nociceptive transmission mediated by glutamate. **C)** The monoclonal antibodies Fremanezumab, Galcanezumab, and Eptinezumab neutralize CGRP and prevent its binding to its receptor. Erenumab binds selectively to the CGRP receptor by blocking its signaling. This leads to the negative regulation of vascular mechanisms and central sensitization mediated by said peptide and its receptor involved in the pathophysiology of migraine.
(IV) or subcutaneously (SC) at a maximum dose of 2000 mg did not cause significant adverse effects nor clinically relevant changes in blood pressure, heart rate, or electrocardiogram parameters compared to placebo.\textsuperscript{40,41} The pharmacokinetic measurements made during these studies showed a half-life of 40 to 50 days after one or two monthly doses regardless of the route of administration.\textsuperscript{41}

Two multicenter, randomized, double-blind, placebo-controlled phase IIb clinical trials demonstrated the safety, tolerability, and efficacy of Fremanezumab for the preventive treatment of both chronic migraine and the management of high-frequency episodic migraine.\textsuperscript{42,43} In the first study (NCT02021773), 264 subjects aged 18 to 65 years with a diagnosis of chronic migraine were randomly assigned to receive one of three treatments: placebo, Fremanezumab SC at an initial dose of 675 mg and two monthly doses of 225 mg, or 900 mg dose monthly. After three months of treatment there was a decrease in the number of hours with headache compared to the baseline level of 37.10 hours (SD 79.44) in the placebo group, 59.84 hours (SD 80.38, p=0.0386) in the group of 675/225 mg, and 67.51 hours (SD 79.37, p=0.0057) in the group of 900 mg. Likewise, there was a decrease in the number of days with moderate to severe intensity of migraine of 4.2 days (SD 6.32) in the placebo group, 6.04 days (SD 6.41, p=0.069) in the 675/225 mg group, and 6.16 days (SD 6.32, p=0.004) in the 900 mg group. Both doses significantly reduced the number of days when the use of an additional drug was necessary to relieve migraine. Adverse reactions were observed in 40%, 53%, and 47% of the subjects in the placebo, 675/225 mg, and 900 mg groups respectively. The majority was not related to the treatment and the most frequent was pain at the site of application and pruritus. No alterations were observed associated with the administration of the antibody in the normal cardiovascular parameters nor in the liver function tests.\textsuperscript{42} In the second study (NCT02025556), the same group of researchers randomly assigned 297 individuals with episodic migraine to receive placebo, 225 mg, or 675 mg of Fremanezumab administered SC for three months. At 12 weeks after starting treatment there was a decrease in the number of days with migraine compared to the baseline of 3.46 days (SD 5.40), 6.27 days (SD 5.38, p<0.0001), and 6.09 days (SD 5.22, p<0.0001) in the placebo, 225mg, and 675mg groups, respectively. Both doses also significantly reduced the number of days with headache of any intensity and the number of days in which it was necessary to use a drug for acute pain relief, as well as days with nausea, vomiting, photophobia, or phonophobia, although the differences regarding the placebo were not spectacular. Nevertheless, both doses of the antibody significantly decreased the score on the Migraine Disability Assessment (MIDAS): 24.23 points (SD 54.56) in the group of 225mg and 24.93 points (SD 62.68) in the group of 675mg with respect to the placebo (9.73 points [SD 55.67]). The most common adverse effects were pain and erythema at the application site, reported in around 50% of all subjects. In this second group of patients, neither changes in cardiovascular parameters nor development of neutralizing antibodies against Fremanezumab were observed.\textsuperscript{43}

Due to the documented safety in the clinical trials described, a new phase III study (NCT02621931) was conducted in a greater number of individuals with chronic headache recruited from nine countries to test the safety and efficacy of this antibody. Of 1130 subjects included in the study, only 1034 completed the trial under three different treatment regimens: 349 subjects received a single dose of 675 mg, 343 received an initial dose of 675 mg and two monthly doses of 225 mg, and 342 received placebo. The results confirmed that the antibody is effective in decreasing the frequency of migraine attacks in patients with chronic headache, since both doses of the treatment reduced the number of days with headache (>4 hours duration, moderate to severe intensity, which required use of triptans or ergotamine), the use of other drugs to treat acute pain, and the scores on the Headache Impact Test (HIT-6) scale. In addition, we observed a greater proportion of subjects who had a decrease of at least 50% in the number of days with headache at one month compared to the baseline: 38% in the group of 675 mg and 41% in the group of 675/225 mg compared with 18% in placebo (p<0.0001).
Adverse effects were reported in 64% of subjects who received placebo, 70% of those who received 675 mg, and 71% in those who received 675/225 mg (see Table 1). Two other phase III clinical trials are being carried out to verify the safety and efficacy of this antibody in the management of episodic migraine (NCT02629861) and in any form of migraine (chronic and episodic, HALO study, NCT02638103); the results were not yet published at the time of writing this review.

Galcanezumab
Galcanezumab (LY2951742) is another completely humanized IgG4 antibody that binds specifically to CGRP. Like Fremanezumab, it showed inhibiting the binding of the peptide with its receptor in vitro and reversing the vasodilation induced by different stimuli in vivo. Likewise, pain was reduced with great efficacy in animal models of osteoarthritis. Phase I clinical trials (NCT02576951, NCT02104765, NCT01337596) showed their safety in different groups of healthy individuals submitted to the administration of the antibody SC in single doses from 1 mg to 600 mg or multiple doses of 150 mg every two weeks, recording a half-life of 29 days.

The first phase IIa study (NCT01625988) to test the safety and efficacy of this antibody in the prevention of episodic migraine (<14 days with pain) was performed in 35 centers in the United States, randomly assigning 218 patients to receive 150 mg of Galcanezumab SC every two weeks for 12 weeks or placebo. The primary objective of the clinical trial was the reduction induced by the antibody in the number of migraine days per month, during the last month of treatment. The study also included an additional 12-week surveillance period after the final dose. The results showed a decrease in the number of days with migraine per month from baseline to week 12 of 4.2 days (SD 3.1) in the group that received Galcanezumab and 3.0 days (SD 3.0) in the placebo group (p=0.003). Likewise, significant decreases in the number of days with headache were observed, as well as a greater percentage of responders with a decrease of at least 50% in the number of days with migraine in the group treated with the antibody with respect to placebo (70% vs 45%; OR 2.88, 90% CI 1.78-4.69). Adverse effects were reported in 72% of subjects who received Galcanezumab and 67% of those who received placebo, the most frequent being upper respiratory infections, injection pain at the site of application, back pain, arthralgia, erythema, and dizziness.

A phase IIb clinical trial (NCT02163993) with this antibody for the prevention of episodic migraine was recently published in the journal JAMA Neurology. This study included 410 subjects who were randomly assigned to receive placebo or one of four doses of Galcanezumab (5, 50, 120, 300 mg) SC once a month for three months. The results showed that the doses of 120 mg and 300 mg were superior to placebo in reducing the number of migraine days per month from baseline, although the 120 mg dose showed a better profile at 12 weeks of treatment, also reducing the score in the Migraine-Specific Quality of Life Questionnaire (MSQ) and the HIT-6 scale, and inducing a higher percentage of responders (reduction of at least 50% in days with pain per month) compared with placebo (75.8% vs 61.9%). (Table 1)

In the most recent study on the effectiveness of Galcanezumab for episodic migraine called EVOLVE-1 (NCT02614183), the observations of the previous investigation were corroborated, but this time with a longer follow-up period of six months and comparing the monthly dose of 120 mg and 240 mg against placebo. This work is not yet available in print but it has been published in a preliminary way on the website of the journal JAMA Neurology. Its most outstanding results are shown in Table 1. Phase III clinical trials with this antibody for the treatment of chronic migraine (REGAIN study, NCT02614261), episodic (EVOLVE-2, NCT02614196), or chronic cluster headache (NCT02397473, NCT02438826 and NCT02797951) have not yet been published.

Eptinezumab
Eptinezumab (ALD403) is a non-sialylated humanized IgG1 antibody that binds selectively to CGRP. The phase I trials that evaluated the safety and pharmacokinetic profile of this monoclonal
antibody were performed in Australia by the company Alder Biopharmaceutical, Inc. The first one was completed in April 2013 and showed that a SC or IV dose of Eptinezumab did not cause significant adverse effects in 104 participants and its half-life was 26-30 days (NCT01579383). The second study was a randomized, double-blind, placebo-controlled phase I trial. The safety of the administration of Eptinezumab was evaluated in 60 healthy volunteers who received the antibody at different doses (100 mg and 300 mg) and by several administration routes (intramuscular [IM], SC, or IV). It was observed that Eptinezumab had comparable levels of suppression of peripheral CGRP with a single monthly dose of 100 mg for 12 weeks either via IM, SC, or IV, without causing significant alterations in liver function or cardiovascular events.49

In a subsequent phase II study (NCT01772524) the safety, tolerability, and efficacy of Eptinezumab for the prevention of episodic migraine in adult patients was demonstrated. They randomly assigned 163 patients to receive placebo or 1000 mg of Eptinezumab IV every two weeks for 12 weeks, with an additional period of three months to evaluate the safety of the treatment. At the end of follow-up, a decrease in the number of days with migraine per month was documented at 5.6 days (SD 3.0) in the 1000 mg group compared with 4.6 days in the placebo group (SD 3.6). Adverse effects occurred similarly in both groups: 52% in the placebo group and 57% in the Eptinezumab group, the most common being upper respiratory tract infections, urinary tract infections, fatigue, back pain, nausea, vomiting, and arthralgia. Notoriously, IV administration of the antibody did not cause reactions at the puncture site.50 Until now, the results of another phase II study started in 2014 have not been published, in which the safety and efficacy of four different doses of Eptinezumab administered IV were evaluated for the treatment of chronic migraine (NCT02275117). Two more phase III studies have already begun. The first one, called PROMISE-1 (NCT02559895), has recruited 900 subjects with episodic migraine to evaluate the quarterly administration of three different doses of Eptinezumab (30 mg, 100 mg, and 300 mg) for 24 weeks. The pharmaceutical company has announced preliminary results of 888 subjects in which it was observed that IV doses of 100 mg and 300 mg significantly reduced migraine days per month presented during the first 12 weeks of treatment in 3.9 and 4.3 days compared to 3.2 days in the placebo group (p=0.0179 and p=0.0001, respectively).51 The PROMISE-2 study (NCT02974153) is in the phase of recruitment of patients with chronic migraine.

**Erenumab**

Erenumab (AMG 334) is a fully humanized IgG2 monoclonal antibody that, unlike the rest, selectively binds to the CGRP receptor in a reversible manner. In phase I studies (NCT01688739, NCT01723514) it was demonstrated that one or multiple doses of SC Erenumab inhibit dermal vasodilation induced by capsaicin, an indicator that there is an interference of the CGRP signaling pathway, without causing significant adverse effects.52,53 The first phase II study conducted with this antibody (NCT01952574) was a multicenter clinical trial in which the efficacy of Erenumab was evaluated for the treatment of episodic migraine. We included 483 subjects who were randomly assigned to receive placebo or 7 mg, 21 mg, or 70 mg of the antibody administered SC once a month for 12 weeks. At the end of follow-up, there was a significant decrease in the number of days per month with migraine with 3.4 days (SD 0.4) in the 70 mg dose group compared with 2.3 days (SD 0.3) in the placebo group. The most common adverse effects were nasopharyngitis, fatigue, and headache both in the treatment group (95%) and in the placebo group (98%). Three percent of the treated subjects developed neutralizing antibodies against Erenumab.54

The second phase II multicenter study conducted with this antibody evaluated its safety and efficacy for the management of chronic migraine (NCT02066415). Erenumab 70 mg, 140 mg, or placebo was administered SC every month for three months to 667 patients. Both doses caused a significantly greater decrease in migraine days at one month (6.6 days) compared with placebo (4.2 days, p<0.0001). Likewise, 40% of the patients...
who received 70 mg of the antibody and 41% in the patients who received 140 mg presented a decrease of at least 50% of the days with migraine per month three months after treatment. Adverse effects occurred with the same frequency in all groups: 39% in the placebo group, 44% in the 70 mg group, and 47% in the 140 mg group; the most common were pain at the site of application, upper respiratory tract infections, and nausea. No abnormalities were reported in vital signs, laboratory results, or electrocardiogram. Eleven subjects in the 70 mg group and three in the 140 mg group developed neutralizing antibodies against Erenumab. A third phase II study to evaluate the safety and efficacy of the same antibody for the treatment of chronic migraine is ongoing and is a continuation of the previously described clinical trial, using the same patients but with a period of treatment and follow-up of 13 months (NCT02174861).

In the first phase III study that was recently published using this antibody (STRIVE, NCT02456740), 955 patients with episodic migraine were recruited and randomized to receive 70 mg or 140 mg of Erenumab or placebo SC every month for six months. At the end of the follow-up, the average reduction in days with migraine per month was 3.2 in the 70 mg group and 3.7 in the 140 mg group, compared with 1.8 in the placebo group. The 50% or more decrease of migraine days per month was achieved in 43.3% of patients in the 70 mg group, 50% in the 140 mg group, and 26.6% in the placebo group (p<0.001 for both treatment groups). The reduction in the number of days of use of specific medications for acute migraine was greater in the groups treated with Erenumab: 1.1 days for 70 mg and 1.6 days for 140 mg, compared to 0.2 days in the placebo group. The physical disability score on the Migraine Physical Function Impact Diary (MPFID) scale improved by 4.2 and 4.8 points in the group of 70 mg and 140 mg respectively, compared to 2.8 points in the placebo group. The rate of adverse effects was similar in all groups: 63% in the placebo group, 57.3% in the 70 mg group, and 55.5% in the 140 mg group. The most common adverse effects were nasopharyngitis, upper respiratory tract infections, and sinusitis. Antibodies against Erenumab were observed in 8% and 3.2% of the subjects treated with 70 mg and 140 mg, however, these antibodies were neutralizing in only one patient.

Finally, the results of the most recent phase III clinical study with Erenumab called ARISE (NCT02483585), in which its effectiveness for the treatment of episodic migraine was evaluated, have been published and are summarized in Table 1. This clinical trial included 577 adults with episodic migraine who were randomly assigned to receive placebo or 70 mg of SC Erenumab monthly for three months. Although the duration of the treatment was shorter than the previous study, the effectiveness and safety of SC administration of the antibody was confirmed. Another phase III study is underway to evaluate the use of Erenumab in patients with episodic migraine from other countries outside the United States and Europe (NCT03333109).

Potential risks, challenges and perspectives

The clinical trials described in this document show favorable results that support the use of the new monoclonal antibodies against CGRP or its receptor for the preventive treatment of high frequency episodic migraine and chronic migraine. Due to their pharmacokinetic profile, these therapeutic agents offer the great advantage of having a long half-life, so that their monthly application would allow a better adherence to the treatment. Evidence of CGRP's role as a facilitator of pain transmission and its distribution within the central nervous system also opens up the possibility of expanding its use for other conditions in which this symptom is an important component, as in pain associated with joint inflammatory processes or other types of headache. In fact, clinical trials are being conducted with the objective of evaluating the benefit of the use of Galcanezumab in the treatment of cluster headache (NCT02397473, NCT02438826, and NCT02797951). Likewise, a recent study in animals has shown that painful stimuli mediated by CGRP inside the lung tissue
exert an immunosuppressive effect that limits the defense responses to respiratory infectious agents, which opens the possibility of using said peptide as a new therapeutic target to improve the course of severe pulmonary infectious diseases.58

However, there are some areas of uncertainty that have yet to be clarified before justifying the preferential use of these antibodies over other treatments currently available. Among them, the concern arises to know the safety of the inhibition of the vasodilator responses achieved with the chronic blockade of the signaling through the CGRP receptor in different vascular beds. Although up to now no alterations in the main cardiovascular parameters have been observed, the follow-up in the clinical trials published in the literature has not been longer than one year and the phase III studies that are being carried out with a longer surveillance period (NCT02985398, NCT03303105, and NCT02959190) will not provide data on the long-term safety of the use of these antibodies, especially in populations with cardiovascular risk factors. It is probable that only phase IV studies offer such information, although being molecules with a long half-life, if a serious level of toxicity arises, it will be difficult to reverse it acutely.

The high incidence of adverse effects among the individuals treated with the different antibodies, especially those administered SC, is also a situation to be considered. Although the proportion of patients who presented an adverse effect during treatment does not differ significantly from placebo and no fatal alterations have been described, some studies describe a percentage of occurrence of up to 70%,38 with pain at the site of application as the most frequent, although in a meta-analysis it was observed that dizziness was the only symptom that occurred significantly more frequently in subjects who received some of the antibodies than in those who received placebo,37 revealing a possible participation of CGRP in the biological mechanisms underlying this symptom.

Another relevant aspect that should be considered is the efficacy shown by the antibodies described here. Although a significantly high percentage of treated patients reduced the number of days with headache per month by at least 50% from basal level, reaching statistical significance, the net difference in this decrease induced by CGRP blockade is not spectacular since it does not exceed two days with respect to placebo in most of the studies. This efficacy is similar to that of onabotulinum toxin A, whose mechanism of action is not specific.10,11 The development of neutralizing antibodies observed in some of the clinical trials could also limit the effect of the treatment in the long term.54-57 In addition, it is expected that the cost of treatment will be high once the marketing of these pharmacological agents is initiated, so before they displace other therapeutic options, new cost-benefit studies should be carried out. Similarly, the widespread use of antibodies against CGRP may not improve the quality of life of all patients because there is evidence to suggest that this peptide would only play an important role in the pathophysiology of migraine in subjects with a predisposition to be sensitive to the effects of it.27 Finally, a limitation of all the clinical trials presented in this review is that the selection criteria of the participants excluded migraine patients who had presented a poor response to other preventive pharmacological measures, who constitute the population that would probably benefit most from the treatment with antibodies. To evaluate this last possibility, clinical trials are already underway in which they intend to learn the usefulness of Fremanezumab (FOCUS study, NCT03308968) and Erenumab (LIBERTY study, NCT03096834) in the management of patients with migraine who have failed treatment with other drugs.
Conclusions

The study of the pathophysiological mechanisms of migraine and the evidence of the participation of CGRP in them have resulted in the development of four monoclonal antibodies against this peptide or its receptor, which have shown a higher efficacy than placebo in the treatment of patients with persistent pain attacks. Although presently this therapeutic possibility seems to be limited to a circumscribed universe of patients with poor response to other drugs, its use in the immediate future should be based on the analysis of the best available scientific evidence and on a cost-benefit balance in order to offer a personalized treatment to the patients most likely to improve their clinical status before displacing other measures that are still useful, since the initial cost is expected to be high. Reviews such as the one presented here provide the theoretical support to facilitate the medical practice and help health professionals responsible for the care of subjects suffering from migraine with their decision-making.

Acknowledgments

To Jorge Camiro Bobadilla and Abigail Vera Vázquez of the Communication Department at CENNM, for their contribution to the graphic content of this manuscript.

Conflicts of interest

There are no potential conflicts of interest for any of the authors in this scientific report.

Funding

The authors have not declared any source of funding for this scientific report.
References


Neurobiology of the perception of social hierarchies: current revision of the literature

Lucía Ester Rizo Martínez. ¹

¹Department of Promotion, Preservation, and Development of Health. University Center of the South, University of Guadalajara.

Abstract

Social hierarchies and their perception are a mechanism of fundamental social organization in many animal species, including human, which has a profound impact on aspects such as survival, social and reproductive behavior and health. Social dominance implies, among other things, the control of some individuals over the other members of the group, as well as greater access to resources. Considering that, from the evolutionary point of view, the social development and the cognitive and emotional processes related to this function are closely related to the development of the brain, the objective of the present review is to describe the neurobiological mechanisms involved in the perception of the hierarchy social, emphasizing the main experimental findings reported.

Keywords

Social hierarchies, perception, neurobiology, review.

Resumen

Las jerarquías sociales y su percepción son un mecanismo de organización social fundamental en muchas especies de animales, entre las que se incluye el humano, lo cual tiene un profundo impacto en aspectos como la supervivencia, la conducta social y reproductiva y la salud. La dominancia social implica, entre otras cosas, el control de algunos individuos sobre los otros miembros del grupo, así como un mayor acceso a los recursos. Considerando que, desde el punto de vista evolutivo, el desarrollo social y los procesos cognitivos y emocionales relacionados a esta función están estrechamente vinculados con el desarrollo del cerebro, el objetivo de la presente revisión es describir los mecanismos neurobiológicos implicados en la percepción de la jerarquización social, enfatizando los principales hallazgos experimentales reportados.

Palabras clave

Jerarquías sociales, percepción, neurobiología, revisión.
Introduction

Social hierarchy and the perception of it underlies social relations between groups and is an important part of the social structure. This has been observed in different species of animals in both simple and complex organisms. Perceiving rank in a social domain is fundamental for an individual’s welfare, even for their survival. The term social dominance is defined as a personality trait which involves a motive to control others, the self-perception of oneself as controlling others, and/or a behavioral outcome resulting from these motives or perceptions.

In functional terms, dominion means that certain individuals have priority access to resources in competitive situations.

In the socio-economic and socio-political human systems, the instances of domination hierarchies are established as monopolies, monarchies, social stratification, caste and class systems, sexism and racism, even in everyday human relationships between parents and children, spouses, siblings, colleagues, and friends, creating conflicts of disharmony.

The determination of hierarchies depends on several factors, from biological aspects to the perception of signals from members of the group. In this way, reaching the top of the social hierarchy depends on the strength of character or personality traits (including courage, perseverance, and motivational drive), as well as a prior history of victory. Domain hierarchies produce marked inequalities in access to resources which can influence quality of life and health.

This study aims to describe the neurobiological mechanisms involved in the perception of social hierarchies through the analysis of studies focused on this topic.

The relationship between the brain and social behavior

Social dominance has been examined from different areas, including the recent studies focused on the role of the brain, highlighting the close dependence between the nature and type of social relationships and the anatomical and functional characteristics of different brain areas, even an underlying innate neural mechanism.

Recent evidence shows that differences in brain structure correlate with the variation in the size of social networks of individuals. From the Darwinian perspective, the evolution of intelligence is linked to life in social groups. The social brain hypothesis states that the development of social expertise was the key to the evolution of the primates’ brain, as a function of coping with the complexities of such a social life. In this sense, Darwin considered that the close relationship between the size of the brain and the development of the intellectual faculties in human beings is supported by comparing of the skulls of the wild races and the civilized races, skulls of the ancient and modern peoples and, by analogy, the whole series of vertebrates.

With respect to ontogenetic development, it is known that, from the first days of life, the human being has a physical mind, a social mind, and a linguistic mind, which enables him to respond effectively and adaptively to the demands in the respective domains. Likewise, it has been observed that the perception of hierarchical dominance is already present in children as young as two years old. Currently, it is...
known that brain development, brain activity, and behavior depend on inherited and environmental influences, and there is a growing appreciation that social information, in turn, can affect the expression and behavior of brain genes.\(^{13}\)

**Genes, hormones, and neurotransmitters involved in social dominance**

In humans and other primates, adverse social environments often translate into long-lasting physiological costs. The strong links between social status and risk of disease in humans suggest that such effects can be particularly accentuated in the primate immune system. The biological mechanisms associated with these effects are fundamental to understanding the evolutionary impacts of social behavior as in the context of human health. Currently, there are few studies aimed at studying how the social state affects gene regulation and the immunological and physiological aspects, especially at the molecular level. However, valuable information has been reported in this regard. For example, it is known that in environments in which hierarchies are strictly applied or subordinates have little social support, the low dominance range can lead to chronic stress, immune compromise, and reproductive dysregulation, with observed changes in the regulation of glucocorticoids, in sex steroid hormones, in serotonergic and dopaminergic signaling, and in the number and proliferation of lymphocytes.\(^{14}\)

**Genes.** Several investigations aimed at studying the genomic and chemical mechanisms underlying social behavior have found that, although the challenges and social challenges facing animals are equivalent in all species, the answers are specific and that these behaviors are regulated by genetic modules and neurochemical codes. Gene-environment interactions and social hierarchies identified in humans and non-human primates influence allelic variants that act by altering gene expression and regulation levels.\(^{15}\) For example, one of the genes considered important in the molecular and cellular aspects of social behavior is egr\(_1\), and the different studies focused on this gene suggest that social experience could trigger changes in larger genetic networks involving many regions in the brain. Likewise, social signals can trigger lasting epigenetic modifications of the genome translated into hereditary changes in the expression of specific genes that are not due to changes in the DNA sequence. It has been found that, for example, in maternal behavior, methylation of the region promoting the glucocorticoid receptor gene of the stress hormone allows NGFI-A, the protein product of the egr\(_1\) gene, to regulate the expression of glucocorticoids, especially in the hippocampus.\(^{15}\)

**Glucocorticoids.** Research conducted in captivity has reported that losing fights can increase glucocorticoid secretion as a general response to stress. Likewise, it has been argued that chronic stress could be the cause of the reproductive suppression of social subordinates. However, recent studies have also suggested that dominant individuals have higher glucocorticoid levels, which may suggest that not only dominated but also dominant individuals with high levels of glucocorticoid are at risk of impaired reproductive function.\(^{17}\)

**Sex steroids and neuropeptides.** Both sex steroids and neuropeptide hormones have been implicitly modulated in all facets of social behavior, including aggression, sexual behavior, parental care, and sociability. On the one hand, sex steroids can affect neural circuits and behavior through genomic mechanisms that involve changes in gene expression, as well as through rapid effects mediated by cascades of signal transduction; on the other hand, neuropeptides exert their actions exclusively through peptides through cascades of signal transduction. It has been observed that hypothalamic peptides oxytocin and vasopressin mediate affiliative and sexual behaviors in several species of mammals. Serotonin is another neurotransmitter related to social behavior, especially social status and dominance in primates. Even selective inhibitors of serotonin reuptake influence social behavior in humans. Serotonin has also been linked to the modulation of aggressive social behavior. The endogenous opioids, in turn, modulate the circuits involved in social bonding, separation anxiety, and gambling.\(^{18}\)
Dopamine. It has been shown that the chronic stress experienced by subordinate monkeys causes a down-regulation of the expression of dopamine D2 receptors. Likewise, with the objective of stipulating predetermined or provoked aspects of the levels of dopamine D2 receptors in monkeys, it was found that the formation of a social hierarchy produced a gradient of dopamine D2 receptors. In the same way, in another study conducted with humans it was reported that there is both the possibility that the serotonin and dopamine systems are modulated by the hierarchical position of an individual, as well as that the level of serotonin in blood also affects the social state of the individual.

Lymphocytes. Chronic activation of the stress response by chronic psychosocial stressors (such as constant proximity to an anxiety-provoking member of the species) may increase the risk of numerous diseases or exacerbate preexisting conditions such as hypertension, atherosclerosis, insulin-resistant diabetes, immuno-suppression, reproductive alterations, and affective disorders. In particular, it has been observed how the stress caused by social dominance produces a profound suppression in the activity and proliferation of lymphocytes. Likewise, it has been reported that social stress desensitizes lymphocytes to regulation by endogenous glucocorticoids, which undoubtedly has a detrimental impact on the physical health of those who suffer from it.

Brain areas involved in social dominance

Some brain regions involved in the perception and learning of social dominance have been identified, which include: the amygdala, the hippocampus, the striatum, the intraparietal sulcus (IPS), the ventromedial prefrontal cortex (VMPFC), and the lateral prefrontal cortex (LPFC), which can be classified into two groups:

I. A group that codes only the social classification and includes:

Lateral prefrontal cortex. This part of the cortex seems to be involved in the perception of social dominance. For example, greater activation of the dorsolateral prefrontal cortex (Brodmann areas 9 and 46) has been observed when participants perceive gestures or faces or images of people with a high rank or social hierarchy compared with those of low social rank.

Likewise, the ventral lateral cortex (mainly Brodmann area 47) has exhibited a greater activation before specifically human social hierarchies. The specificity of this brain region is unknown, but it is hypothesized that it could have a relationship with the attentional system based on evidence from previous studies. The great activation observed in the ventral lateral cortex during social interaction with socially dominant persons is very likely to reflect a great intensity of attention.

The lateral prefrontal cortex also plays an important role in compliance with social norms.

With respect to the functional differences of the lateral prefrontal cortex and the ventral lateral prefrontal cortex, it has been suggested that they participate in different cognitive demands; however, this position is still unclear at present.

Amygdala. The role of the amygdala has been reported in different measures aimed at the study of social dominance, such as a) the detection of interpersonal distance, b) the nature of a hierarchy (stable or unstable) or the context of a classification (social or not social), c) during the inference of social classification.

Anterior hippocampus. The anterior part of the hippocampus (which has connections with the amygdala) is related to the level of individual confidence with respect to the inference of social classifications.

II. A group related to social dominance and that codifies social and non-social hierarchies and is formed by:

Ventromedial prefrontal cortex. Some studies have shown that this part of the cerebral cortex seems to have a specific role for the perception of social dominance.
of clues of dominance.\textsuperscript{26,35} One study showed how patients with lesions in the ventromedial cortex are insensitive to specific perceptual cues of social hierarchical value such as age and gender.\textsuperscript{35} Likewise, a correlation has been found between the activity of the ventromedial cortex and the social and non-social hierarchies.\textsuperscript{33}

**Intraparietal sulcus.** The participation of the intraparietal sulcus in the attentional orientation related to the perception of dominance has been observed. It has also been observed there is participation of this brain area in processing information related to “rank” independently of content (social or non-social), as well as with the “magnitude.”\textsuperscript{25,36,37}

**Striatum.** Zink et al\textsuperscript{25} found that seeing the face of a higher-ranking opponent causes a greater degree of activity in the ventral striatum than when seeing the face of a lower-ranked opponent. They also reported increased activation of the striatum when participants were informed of their victory or loss and when they defeated a superior human player. However, this activation did not occur when the participants defeated a superior computer player (non-social context). From another study, it was concluded that striatal activity can encode a social classification based on a biased sensitivity related to the participant’s hierarchical status.\textsuperscript{38}

**Posterior hippocampus.** It has been related to social and non-social classifications.\textsuperscript{33}

**Brain circuits involved in social dominance**

Currently, the neural circuit mechanism underlying social dominance is considered practically unknown.\textsuperscript{7} The main systems and circuits in the vertebrates proposed by some authors are described next.

a) The mesolimbic reward system, whose main characteristic lies in its massive dopaminergic projections from the ventral tegmental area to the nucleus accumbens, and includes brain areas such as the lateral septum, the ventral pallidum, the striatum, the basolateral amygdala, the nucleus of the stria terminalis and the hippocampus.\textsuperscript{15} Many studies indicate that through the mesolimbic reward system, the individual evaluates the relevance of the stimuli in order to generate an adaptive response.\textsuperscript{39,40} Likewise, this system also mediates an individual’s ability to adapt to chronic social stress.\textsuperscript{41}

b) The so-called “social behavior network,”\textsuperscript{42} which includes the lateral septum, the extended medial amygdala (i.e. medial amygdala and the bed nucleus of the stria terminalis), the preoptic area, the anterior hypothalamus, the ventromedial hypothalamus, and the periaqueductal gray matter.

All of these areas are reciprocally connected and express sex steroid receptors. The investigations carried out to date with respect to the functions of this network have evidenced their role in the mediation of sociability between species, as well as in paternal and maternal behavior.\textsuperscript{43,44}

c) Circuit controlled by the prefrontal cortex. Some studies in which brain imaging technique was used in humans have reported the involvement of the dorsolateral and medial prefrontal cortex in social dominance behaviors.\textsuperscript{25,37} The participation of this area underlies the cognitive functions that imply the recognition of the social condition, the learning of social norms, and the detection of the violation of the social norms involved in this function.\textsuperscript{5} Likewise, with the objective of knowing where and how the information of social hierarchy in the brain is encoded, a study\textsuperscript{7} was carried out through a paradigm of social dominance in mice and they found that there is a circuit controlled by the medial prefrontal cortex, in particular, the dorsal area, for the hierarchy of dominance. Through the projections of the medial prefrontal cortex to regions such as the dorsal raphe, the ventral tegmental area, the hypothalamus, and the amygdala, it exerts descending controls on the release of serotonin and dopamine, endocrine function and the response to fear which could contribute to the key characteristics.
of domination behaviors, including aggression and the ability to respond to stress and fear. In particular, these researchers found that dominant mice have greater excitatory synaptic strength in the pyramidal neurons of the V layer than their subordinates, as well as a significantly greater number of positive c-Fos neurons in the prelimbic region of the medial prefrontal cortex.

**Neuroanatomical markers of the social hierarchy: studies with cerebral imaging and electroencephalogram**

It has been reported that in several species, including humans, facial signals are used to express social dominance and submission, which are usually of two types: emotional expressions related to aggression and facial postures that vary in the look and in the vertical orientation of the head. The perception of dominance is related to facial expressions of anger, a sign of threat or possible aggression, a direct gaze, and an upward tilt of the head, while submission is conveyed with a fearful expression and facial postures with a fixed gaze and a downward tilt of the head. On the other hand, it has also been suggested that, in stable social hierarchies, the facial postures used by individuals are more neutral, regardless of dominance or submission.

Considering the evolutionary importance of social dominance, it is interesting to know the cerebral mechanisms underlying the recognition of this function in humans; however, to this day, there are few studies carried out in this regard.

For example, a study was conducted through potential techniques related to events and functional magnetic resonance in which the neuronal mechanisms underlying the perception of social dominance from facial signals were examined. They found that the perception of mastery of emotional expressions related to aggression occurs early in neuronal processing, while the perception of social dominance of facial postures emerges later. Brain imaging results show that the activity in the fusiform gyrus, superior temporal gyrus, and lingual gyrus, is associated with the perception of social dominance of the facial postures and the magnitude of the neural response in these regions differentiates between the perceived dominance and the perceived submission. Likewise, another study was conducted with the objective of determining the neuroanatomical bases in the inference of the hierarchical identity using the techniques of event-related potentials and structural magnetic resonance during the application of a computerized game in which the participants visually discriminated simulated players. One of these players performed successfully and, through different manipulations, often confirmed high status. Another simulated player presented an unsuccessful performance, exhibiting a lower rank. The participants showed a greater amplitude in the N170 component related to the perception of the image of a superior player compared to an inferior player, which was correlated with the cerebral morphology of the posterior cingulate cortex, the superior temporal gyrus, the insula, the fusiform gyrus, and the caudate nucleus.

On the other hand, with respect to the electroencephalographic technique, the perception and interpretation of social hierarchies has frequently been related to modulation in the alpha band be it with the decrease and increase of this band in the right and left prefrontal cortex, with a great reduction at the perception of faces that represent a high social rank, or with an asymmetry correlated with self-reported dominance.
Conclusions

Although there are currently few studies focused on determining the neurobiological mechanisms involved in social hierarchy and its perception, the evolutionary relevance of this function in the social relationships of individuals is evident, even suggesting an underlying innate neural mechanism. The genes, hormones and neurotransmitters that modulate the perception of social dominance have been determined in some way, however, more studies are still needed to explore these topics. It is also necessary to expand the research focused on determining the cerebral areas underlying the social hierarchy, which, according to what has been reported so far, include the prefrontal, parietal, temporal cortex, the striatum, the hippocampus, the amygdala, as well as the reward circuit, the so-called social behavior network, and another circuit controlled by the prefrontal cortex. Undoubtedly, conducting research using techniques such as brain imaging, electroencephalogram, etc., will allow us to know more about the cerebral mechanisms related to this important social function.

Acknowledgments

Manuscript made during the support of CONACYT through the Program for Retention.

Conflicts of interest

There are no conflicts of interest on the part of the author of this scientific manuscript.

Funding sources

This scientific manuscript was made by the author during the year during which she was a beneficiary of the CONACYT Program for Retention.
References

Review

Periodic electroencephalographic patterns: a controversial and infrequent finding

Liane Aguilar-Fabré,1 René Francisco Rodríguez-Valdés.1


Abstract

Periodic electroencephalographic patterns are discharges usually epileptiform in appearance, which occur at regular intervals associated with acute brain injury such as cerebral vascular disease and encephalitis. They are commonly classified as periodic lateralized epileptiform discharges, periodic lateralized epileptiform discharges bilateral independent, generalized epileptiform discharges, triphasic waves and stimulus-induced rhythmic, periodic or ictal discharges. The aim of this study is to make a review of the periodic EEG patterns, emphasizing the importance of their recognition and clinical significance. The clinical significance of the periodic EEG patterns is uncertain, it is related to a variety of etiologies and suggest that these patterns are unequivocally epileptogenic in some cases and these patterns associated with poor prognosis. Their recognition and classification are important to establish an accurate correlation between clinical, neurological, laboratorial and neuroimaging data with the EEG results, which allow making adequate therapeutic benefit of critical patient behavior.

Keywords

Periodic electroencephalographic patterns, periodic epileptiform discharges, generalized epileptiform discharges, triphasic wave.
Los patrones electroencefalográficos periódicos (PEP) son descargas con apariencia epileptiforme que aparecen a intervalos regulares asociadas a una lesión cerebral aguda como la enfermedad cerebrovascular y las encefalitis. Estas descargas se producen a intervalos regulares y se clasifican comúnmente como: descargas epileptiformes lateralizadas periódicas, descargas epileptiformes lateralizadas periódicas independientes bilaterales, descargas epileptiformes generalizadas, las ondas trifásicas y las descargas ictales o periódicas rítmicas inducidas por estímulos. El objetivo de este trabajo es hacer una revisión de los patrones electroencefalográficos periódicos, haciendo énfasis en la importancia de su reconocimiento y su relevancia clínica. La importancia clínica de los patrones periódicos en el electroencefalograma es incierta y está relacionada con diversas etiologías. Algunos autores sugieren que estos patrones son inequívocamente epileptogénicos y se asocian con pronósticos desfavorables. Su reconocimiento y clasificación es importante para establecer una correlación exacta entre los datos clínicos, neurológicos, de laboratorio y de neuroimagen con los resultados del electroencefalograma, lo cual permitiría establecer conductas terapéuticas adecuadas en beneficio del paciente crítico.

Palabras clave
Patrones electroencefalográficos periódicos, descargas epileptiformes periódicas, descargas epileptiformes generalizadas, ondas trifásicas.

Corresponding author:
Liane Aguilar Fabré
Nervous System Clinic Department of Biomedical Research
Autonomous University of Querétaro, School of Medicine
Calle Clavel No. 200, Col Prados de la Capilla; Querétaro, Qro. México. CP 76170
Phone: (442) 192-1200 ext: 6252
E-mail: aguilarfabre@yahoo.com
Introduction

Periodic electroencephalographic patterns (PEPs) are always an abnormal finding on the electroencephalogram (EEG). PEPs consist of discharges with diverse forms, which usually have an epileptiform appearance and occur with a regular frequency or at regular intervals intermittently.

These patterns are usually classified as periodic lateralized epileptiform discharges (PLEDs), bilateral independent PLEDs (BIPLEDs), generalized periodic epileptiform discharges (GPEPs), triphasic waves, and stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIEDs).

The term PLEDs was introduced in 1964 by Chatrian et al., although the phenomenon was described for the first time in 1952 by Echlin et al. PLEDs are a relatively infrequent electroencephalographic pattern characterized by the presence of spike-and-wave complexes, or lateralized sharp waves or focal periodic or quasi-periodic present in most or all of the records.

The purpose of this review is to emphasize the importance and clinical significance of PEPs, considered controversial and infrequent. These patterns may be present in critically ill patients who need therapeutic interventions based on decision-making resulting from their interpretations, which is why we consider the approach of this topic of great importance.

Search strategy and selection criteria
A PubMed/MEDLINE search was performed using the following terms and phrases (combining two with the Boolean operator “and”): periodic epileptiform discharges, electroencephalography, PLEDs, BIPLEDs, GPEPs, triphasic wave, clinical significance, etiologies.

The following limits were established: “only items with links to free full text, Humans, Meta-Analysis, Practice Guideline, Review, English, Spanish, published in the last 10 years.”

On some occasions, publications cited in the articles initially selected were included, regardless of the year of publication, provided they presented current and important information for the development of the review. Only those articles in which the full text could be reviewed were used as references. Those that were considered to have important methodological deficiencies, that were not adequate to the specific topic, or which presented information that had been covered sufficiently in other texts that were considered of higher quality or more recently updated, were discarded.

Periodic Lateralized Epileptiform Discharges (PLEDs)
PLEDs are the most common PEP. These are spike-and-wave complexes followed by slow waves that repeat every 1 to 2 seconds. The periodic complexes are limited to a focal cerebral area (often a hemisphere). PLEDs have a frequency of 0.2-0.3 Hz, are often biphasic, triphasic, or polyphasic, and are associated with a localized attenuation of base activity between discharges. Periodicity is what characterizes this electroencephalographic pattern, generally varying less than 20% in the same subject but able to vary significantly between one patient and another. In 1950, Cobb attributed the periodicity of the discharges to a disconnection between the cortex and subcortical structures caused by a white matter lesion. However, through experimental studies, Chatrian showed that any injury could be associated with PLEDs. The prevalence of PLEDs in the routine EEG varies between 0.1% and 1%.

They are observed in the context of multifocal or diffuse brain lesions such as anoxia and they announce an unfavorable prognosis associated with a higher mortality. Approximately 80% to 90% of patients with PLEDs experience clinical seizure activity, mainly focal motor seizures. In 1991, Reiher et al. described the “PLED plus” entity characterized by PLED mixed with polyspikes of high frequency and low voltage. These have a stronger correlation with the presence of clinical crises and status epilepticus. PLEDs are generally not considered an ictal pattern, although this has...
been reported and remains a subject of ongoing debate.\textsuperscript{10,11}

**Bilateral independent periodic lateralized epileptiform discharges (BIPLEDs)**

Bilateral PLEDs which occur independently (BIPLEDs) were recognized by Chatrian in 1964,\textsuperscript{2} and characterized by de la Paz and Brenner in 1981.\textsuperscript{12}

BIPLEDs occur when PLEDs are viewed in both hemispheres independently and asynchronously. This pattern is less common than PLEDs and is highly associated with the occurrence of seizures in patients with acute diseases.\textsuperscript{13} Unlike PLEDs, BIPLEDs can be presented as asynchronous complexes that usually differ in morphology, amplitude, frequency of repetition, and topography.\textsuperscript{14} Some studies report an incidence of BIPLEDs of 4 to 22\% in the ICU and a prevalence of 0.1 in the routine EEG.\textsuperscript{2,6,15}

A study by Fitzpatrick\textsuperscript{6} in 21 patients with BIPLEDs showed a mortality of 52\% and a study conducted by de la Paz\textsuperscript{12} showed a mortality of 61\%.

BIPLEDs are typically associated with acute structural injury with or without metabolic disorders.\textsuperscript{12,13,16} The most common cause of BIPLEDs is anoxic encephalopathy and central nervous system infections, with a high incidence of coma.\textsuperscript{12,16}

**Generalized Periodic Epileptiform Discharges (GPEDs)**

Periodic discharges are defined by a “repetition of a waveform with a relatively uniform morphology and duration, with a quantifiable interdischarge interval between consecutive waveforms, and recurrence of the waveform at nearly regular intervals,” where waveforms are characterized by a duration of 0.5 s or less or limited to three phases.\textsuperscript{17}

GPEDs occur in both hemispheres symmetrically, diffusely and synchronously.\textsuperscript{4} GPEDs are classified taking into account the interval between short and long discharges. Diffuse periodic discharges with short intervals (periodic short-interval diffuse discharges, PSIDDs) are those whose duration of the interval is between 0.5 and 4 sec. They occur in hypoxic or hepatic encephalopathies, drug toxicity, and neurodegenerative diseases such as Jakob Creutzfeldt disease.\textsuperscript{4} PSIDDs are associated with toxic-metabolic encephalopathies and anoxic brain damage and related to a fatal evolution and severe neurological sequelae, especially those associated with repetitive myoclonic jerks. Diffuse periodic discharges with long intervals (periodic long-interval diffuse discharges, PLIDDs) are those whose duration of the interval is between 4 and 30 sec.\textsuperscript{18}

In a standard 20-minute EEG record, the incidence of GPEDs is approximately 1\%,\textsuperscript{19,20} occurring in approximately 20\% of patients in a coma due to a severe postanoxic encephalopathy after cardiac arrest.\textsuperscript{21-23} Typically presenting in the first 12 to 48 hours after resuscitation.\textsuperscript{24,25} Other causes are diffuse metabolic encephalopathy,\textsuperscript{16,26} including encephalopathies associated with sepsis,\textsuperscript{19} acute brain damage, and cerebrovascular accident.\textsuperscript{23,27}

An example of generalized periodic epileptiform discharges can be seen in Figure 1.

**Triphasic waves**

Generalized periodic discharges also include triphasic waves, a pattern initially described in 1950 by Foley.\textsuperscript{28} This term was coined in 1955 by Bickford\textsuperscript{29} in reference to their typical morphology characterized by three phases. They consist of periodic generalized acute waves or strongly contoured delta waves with a triphasic morphology (typically with a negative-positive-negative polarity, with a duration of each phase longer than the previous one), which are repeated between 1.0 and 3.0 Hz.

Triphasic waves are periodic and generalized, usually have a frontal predominance and do not always have an epileptiform appearance (a reason why they are often not included in the GPEDs category).\textsuperscript{4,13} This pattern can occur in any toxic metabolic or structural encephalopathy, although the first descriptions were associated with hepatic
Recent studies by Foreman\textsuperscript{32} conclude that the triphasic wave is a clinically ambiguous electroencephalographic descriptor that is not reliable in the prediction of seizures or in the presence of toxic-metabolic encephalopathy. An example of triphasic waves can be seen in Figure 2.

**Rhythmic ictal or periodic discharges induced by stimuli.**

These EEG patterns were first described by Hirsch in 2004,\textsuperscript{33} observing that by stimulating patients in a coma or stupor, EEG patterns of ictal appearance were obtained. These were referred to as stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs). The SIRPIDs are considered periodic when it comes to recurrent epileptiform discharges at regular or almost regular intervals, with an identifiable inter-discharge interval. Some patients with clinical seizures have SIRPIDs, especially focal motor seizures, but this pattern is usually purely an electroencephalographic change that is not accompanied by obvious clinical manifestations. The pathophysiology, clinical, therapeutic, and prognosis of the SIRPIDs is not yet well defined.\textsuperscript{13,33,34}

**Etiology**

The PLEDs suggest an acute brain dysfunction of diverse etiology or a unilateral brain injury, usually of a destructive nature. This pattern has been described in patients with cerebrovascular accidents, rapidly growing brain tumors such as glioblastoma multiforme, brain abscesses, viral encephalitis, Jakob Creutzfeldt disease, bruising, and less frequently in patients with demyelinating diseases, anoxia, primary epilepsy, and migraines, among others.\textsuperscript{13,35-39}

In cases of cerebral infarction, PLEDs are obtained in the area adjacent to the infarction. This area is partially affected by the disease but is still capable of generating electrical activity. Some authors emphasize the importance of the presence of structural brain injury associated with metabolic disorders in the production of PLEDs.\textsuperscript{13,40,41}

BIPLEDs and GPEDs are associated with diffuse or multifocal brain damage as occurs in anoxia and announce an unfavorable prognosis with high mortality.\textsuperscript{4,6,12,42}

A study conducted by Orta\textsuperscript{16} reported that approximately 45\% of patients with periodic

---

**Figure 1.** Generalized epileptiform discharges in a male 8-year-old patient with herpetic viral encephalitis.

![Figure 1](image-url)
epileptiform discharges presented evidence of an associated acute etiology, particularly patients with BIPLEDs and GPEDs. On the other hand, there was a statistical association between acute etiology and a higher probability of death only in those patients who had PLEDs. However, patients with BIPLED and GPED had a higher mortality (29% -39% vs 24%) than the PLED group.

Some authors have studied the association of GPEDs with structural damage. Structural changes have been observed in approximately 78% of patients with GPEDs, most have found a predominance of subcortical lesions typically in subcortical gray matter either alone or in combination with cortical lesions. The absence of structural lesions in magnetic resonance imaging has been reported in 20-25% of patients with GPEDs.

Evolution
PLEDs are usually associated with acute-subacute presentation of the underlying disease process. In patients with chronic brain diseases, PLEDs are usually observed during an acute process. The PLEDs are transient and resolve spontaneously between two to three weeks, the discharges tend to decrease in amplitude and distance until they disappear.

Chronic PLEDs have been reported in patients with chronic epilepsy, during alcohol withdrawal or in chronic toxic metabolic syndrome. Many authors consider PLEDs the reflection of acute brain damage associated or not with seizures depending on many factors, such as individual propensity, the existence of underlying processes and the coexistence of metabolic disorders. The evolution is more related to the age of the patient and the etiology than to the specific periodic pattern.

Gurer reported that 7% of the 71 adults studied exhibited chronic PLEDs and that chronic lesions were found in 35% of these patients. Fitzpatrick showed a similar incidence of 10% attributable to the presence of a cortical dysplasia or a severe distant brain injury, all had partial seizures. Fushimi described a patient who presented bilateral PLEDs for more than six months and stated that there were no notable symptoms except for a slight deterioration of memory. Da Silva and Bartolucci reported that the PLEDs disappeared before four days in most of their patients and that this pattern was replaced by the

**Figure 2.** Triphasic waves in a male 65-year-old patient with hepatic encephalopathy and a consciousness disorder.
appearance of a slow base activity, delta rhythms, voltage suppression periods, and focal paroxysmal activity.

**Ictal vs. interictal pattern**

Garzón performed a prospective study in 55 patients, with a total of 62 epileptic status and 254 ictal/postictal EEG records and analyzed the relationship between PLEDs and status epilepticus. This researcher showed that although PLEDs were not always associated with seizures and status epilepticus, it could be unequivocally an ictal pattern. An increase in focal glucose metabolism has been shown to be associated with PLEDs, reinforcing their probable epileptogenic nature.

Other investigators consider the PLEDs an interictal change or an unstable ictal-interictal continuum; although their pathophysiology is unknown, they could indicate an ictal pattern in some cases. Studies have reported that PLEDs are generally associated with the state of clouding in 95% of patients, focal seizures and neurological signs in 80%, and a continuous partial epilepsy in 30% of patients. A study conducted by Snodgrass reports clinical seizures or status epilepticus in the course of the disease in 90% of patients: 50% presented a partial motor status epilepticus, 22% partial motor seizures, 6% continuous partial epilepsy, 6% isolated generalized seizures, and 8% generalized epileptic state.

Seizures that occur in patients with PLEDs may be partial, generalized sensorimotor seizures, complex partial epileptic status, and continuous partial epilepsy. PLEDs plus and BIPLEDs plus have stronger correlations with clinical crises and status epilepticus. Foreman demonstrated a strong association between non-convulsive status epilepticus and GPEDs while the presence of triphasic waves has a low association with the development of epileptic seizures.

Baykan reported that the extension of PLEDs is also important with respect to the association with seizures. Their results showed that PLEDs that appeared prominent on one side but with a slight contralateral spread had a stronger relationship with status epilepticus or with frequent recent seizures than when PLEDs presented a very strict location.

The pathophysiological processes underlying the PLEDS are still controversial. Some studies have reported hypermetabolism and hyperfunction in the PLED centers studied through PET and SPECT respectively. Hypermetabolism is a condition usually associated with ictal patterns, PLEDs, in this case, represent a partial epileptic state. Assa came to a similar conclusion, that hyperperfusion was probably related to partial epileptic status. Other authors through studies conducted with SPECT and IMR concluded that this pattern was probably ictal. The increase in cerebral focal blood flow and metabolism found during PLEDs is in contrast to the hypometabolism usually seen during interictal discharges. Finally, Singh concluded that the pattern was ictal and that it should be considered as an epileptic state due to the presence of a continuous pattern, it would also be a continuous partial epilepsy. Many authors consider it a non-convulsive status epilepticus, a subtle status, or a partial status epilepticus.

Nei reported that PLEDs are the only characteristic of the EEG related to a poor prognosis in epileptic status regardless of the etiology. Snodgrass found that most EEGs with PLEDs were obtained within the first four days with convulsive activity or epileptic status and postulated that the phenomenon of PLEDs in the EEG could be considered as the final stage of epileptic status.

PLEDs can be considered as an electroencephalographic activity closely associated with recent seizures, which is a manifestation of an increase in neuronal excitability caused by various etiologies. A study by Orta reports that the absence of seizures at the beginning (acute etiology) was associated with death.
PLEDs should be verified in patients in intensive care units who do not recover their usual alert level. If there is severe brain disease in the terminal phase, then medication with antiepileptic drugs should not be considered.

Some authors have reported that antiepileptic medication has been effective. Terzano\textsuperscript{61} reported that carbamazepine (CBZ) was effective, concluding that acute PLEDs can represent a non-convulsive status epilepticus. In this same study, the authors observed that patients did not respond adequately to mental tests when the frequency of discharge of PLEDs was 2/sec, 25% responded correctly when the frequency was 0.5/sec, and significantly 80% responded correctly when there were no PLEDs. Corda\textsuperscript{62} also used CBZ to normalize the “electroclinical state.” Medication with barbiturates and phenytoin has not been very helpful, however, good responses to treatment with sodium valproate and felbamate have been reported, resulting in the abolition of PLEDs.\textsuperscript{63,64}

In certain medical conditions, specific medications not considered antiepileptic drugs can be effective. For example, in a patient with herpes simplex encephalitis, acyclovir was administered and the PLEDs disappeared.\textsuperscript{65} In a case of meningoencephalitis, corticosteroid therapy was dramatically effective.\textsuperscript{66} In the case of PLEDs associated with multiple sclerosis, intravenous steroids are needed for complete recovery, although standard antiepileptic drugs are partially effective.\textsuperscript{67}
Conclusions

The clinical importance of PEPs remains uncertain and controversial. PEPs are seen in a wide range of etiologies and they are electrographically heterogeneous. Therefore, patients should be carefully investigated for infectious, toxic-metabolic, and/or intracranial lesions, and a non-convulsive status epilepticus should be considered. Its recognition is important to try to establish an exact correlation between the clinical, neurological, laboratory, and neuroimaging data with the results of the EEG and to guide the therapeutic decisions.

Conflicts of interest
The authors declare that there are no potential conflicts of interest to report regarding this scientific report.

Funding sources
The authors have not declared any source of funding for this scientific report.
References


Periodic electroencephalographic patterns


Review

Neuronavigation: Image-Guided Neurosurgery

Neuronavegación: neurocirugía guiada por imagen

Abstract

Accuracy is an essential aspect in the performance of brain surgeries that has been focus of intense clinical research over the history of neurosurgery which have resulted in the development of novel technologies for the localization of intracranial and spinal cord lesions. The advent of new neuroimaging techniques as well as the increasing availability of tools for spatial orientation have improved the ability of neurosurgeons to trace deep brain structures with precision and to perform surgical procedures with the minimum risk. Neuronavigation constitutes a technology incorporated to the neurosurgery practice that allow real-time visualization of tridimensional reconstructions from intracranial structures obtained by preoperative imaging studies on a computer screen, which facilitates the approach to different physiological and anatomical cerebral abnormalities with a higher precision compared with that achieved by other conventional techniques. Its increasing availability forces physicians responsible for the care of patients with neurological disorders potentially candidates for surgery to know the operative technique, principle and applications of neuronavigation as well as advantages and disadvantages offered by such technology for the treatment and prognosis of several cerebral diseases.

Keywords

Neuronavigation, neurosurgery, stereotaxic, cerebral tumors, intraoperatory magnetic resonance imaging.
Resumen

La precisión es un aspecto fundamental en la realización de la cirugía neurológica que ha sido motivo de intensa investigación durante la historia de la neurocirugía y ha resultado en el desarrollo de tecnologías para la localización de lesiones intracraneales y de medula espinal. El advenimiento de nuevas técnicas de imagen cerebral, así como la disponibilidad de herramientas de orientación espacial han mejorado la capacidad de los neurocirujanos para acceder con exactitud a estructuras cerebrales profundas y realizar operaciones exitosas con el menor riesgo. La neuronavegación constituye una novedosa tecnología incorporada a la práctica de la neurocirugía y permite una visualización en tiempo real de las estructuras intracraneales en un monitor de computadora a partir de reconstrucciones en tercera dimensión obtenidas por estudios de imagen preoperatorios, lo cual facilita el abordaje de diferentes alteraciones fisiológicas y anatómicas cerebrales con una precisión mayor a la lograda por técnicas convencionales. Su creciente disponibilidad obliga a los médicos encargados del cuidado de pacientes con alteraciones neurológicas potencialmente candidatos a cirugía al conocimiento de la técnica, el principio y las aplicaciones de la neuronavegación, así como de las ventajas y desventajas que ofrece dicha tecnología para el tratamiento y pronóstico de diversas enfermedades cerebrales.

Palabras clave
Neuronavegación, neurocirugía, estereotaxia sin marco, tumores cerebrales, resonancia magnética nuclear intraoperatoria.

Corresponding author:
Parménides Guadarrama Ortíz
Departamento de Neurocirugía, Centro Especializado en Neurocirugía y Neurociencias México, Hospital Trinidad, Tlaxcala esquina con Manzaniilo, Roma Sur, Ciudad de México.
Teléfono: 55 3666 5317
E-mail: dr.guadarrama.ortiz@cennm.com
Introduction

Have you driven a car in another country or in a different region of your city that you had never visited before? If it were not for technologies such as GPS, you would have surely had to drive around and take wrong turns before reaching your destination. The same thing happens when there is a small brain injury located in a deep region inside the skull. Although most neurosurgeons have sufficient knowledge of the internal structure of the brain as a result of their extensive anatomical knowledge and experience in the surgical field, patients sometimes present alterations that constitute a challenge due to their location, which requires careful planning of the approach and the route to reach the injury.

Precision in the surgical approach has been a preoccupation since the beginning of brain surgery and for many years it has also constituted a continuous research focus for the development of new useful tools for the location of intracranial lesions. This development has always been dependent on the availability of imaging techniques capable of offering an anatomical view of brain tissue, so the advent of new imaging tools has been accompanied simultaneously by improvements in guidance methods and neurosurgical approach. At the beginning, ventriculography (injection of a contrast medium in the ventricular system) was used as a technique to locate and resect lesions near the ventricular cavities that had sufficient volume to deform these structures and thus demonstrate their position with respect to them. Subsequent attempts resulted in the invention of rigid stereotactic reference frames that had originally been used for animal experimentation and were placed around the patient’s skull, fixed to it, so that they remained immobile during surgery. The frames contained different systems of Cartesian coordinates that allowed to determine the location of intracerebral structures taking as reference points on the surface of the cranium or in deep sites such as the Turkish seat and the foramen of Monro brought to light by the emergence of radiography and ventriculography, respectively. A historic achievement for medicine and neurosurgery was the invention of sophisticated technologies such as computerized axial tomography (CAT) and nuclear magnetic resonance imaging (NMRI) that allowed obtaining more complete images of cranial bone and brain tissue, as well as their 3D reconstruction from cuts at different brain levels. This was translated into greater precision and better clinical results after the resection of tumors and vascular lesions guided by the use of stereotactic frames that are still in use today given their effectiveness.

However, none of the tools available was able to show in real time the maneuvers performed by the surgeon and superimpose them on the brain images to guide the surgery with precision. In addition, the stereotactic technique had several disadvantages that made the surgical procedure difficult because the reference frame limited the range of maneuver and the visibility was also subject to a high degree of obstruction. Until a few years ago there was no tool that could help the doctor accurately locate different structures inside the skull and perform surgery with minimal risk of damage without the need for a stereotactic frame until image-guided surgery, frameless stereotaxis, or “neuronavigation” was developed.

The first surgery performed with the support of a neuronavigation team was carried out in 1986 by Roberts and his collaborators, using a neuronavigator that superimposed three-dimensional reconstructions of images obtained by CT in the visual field of the microscope, calculating the orientation and position of the latter thanks to a system based on acoustic waves. This technology has had improvements over the past two decades and currently uses information from imaging studies such as CAT or NMRI to upload it to a computerized system in which it is possible to perform three-dimensional reconstructions of brain tissue, superimpose the images of functional studies, and plan the surgical approach. Subsequently, the neuronavigation team integrates spatial
information through optical or electromagnetic sensors that detect and locate different reference points placed on the patient's skull and whose function is very similar to GPS. It creates a brain map allowing specific points to be located inside the skull, as well as observing the movements of the surgeon superimposed on the brain images in real time or projecting and superimposing the imaging information in the visual field of the microscope. This fact facilitates the planning of the site where the brain will be entered and the structures that will have to be avoided on the way to a lesion or damaged structure without the need to perform a wide craniotomy. For this purpose, the navigation system includes a computerized image processing module, a reference frame or antenna, an optical or electromagnetic detector, and a pointer that is recognized by the detector. (Figure 1)

**Figure 1. Elements that make up the neuro-navigation system.**

The neuro-navigation system consists of a frame of reference or antenna (A) and a pointer (B) and fiducial markers in place (C), which are spheres that reflect the infrared light emitted by the control center (D). The control center is composed of a computer system to which the data of imaging studies are loaded with reconstructions in 3D to display them on a screen, as well as a tower with two light emitters that function at the same time as detectors of the signal reflected by the fiducial markers placed on the pointer and on the antenna. To visualize in real time the position of the surgical instruments on the screen while the surgeon performs the operation, the fiducial markers can also be placed on the instruments (E and F).
Technique

Obtaining brain images

The first step for the procedure is obtaining the brain images to perform a 3D reconstruction. The imaging technique to be used depends on the availability of the resource as well as the precision required for each surgery. In addition, images obtained by different techniques can be superimposed to achieve a reconstruction with the greatest possible anatomical detail. For example, CAT has a greater capacity to evaluate bone structures compared with NMRI, while the latter is superior in obtaining high definition images of soft tissues. The superposition of the information coming from both techniques can provide great detail of the bone tissue and at the same time an optimal image of the cerebral structures. Furthermore, the performance of intravenous contrast imaging techniques such as CT or MR angiography is useful for adding information of cerebral vascular anatomy in the approach of arteriovenous malformations, aneurysms, and other vascular anomalies.

Finally, the increasing availability of functional NMRI and diffusion tensor imaging (DTI) tractography allow locating the eloquent areas and subcortical tracts in such a way that it is possible to superimpose them on anatomical reconstruction and thus plan the surgical approach. For this purpose, neuronavigation can also be combined with cortical mapping by electrostimulation.

Digitization of spatial information by recording anatomical landmarks

To correlate the imaging reconstructions with the spatial information of the patient, the neuronavigation team must obtain coordinates from different reference points located on the skull as well as in several locations within the surgical field and on the instruments that will be used during the surgery. For this purpose, a record of anatomical reference sites is made by placing a pointer on the surface of the skull which has reflecting or fiducial spheres that reflect the ultraviolet light waves emitted by light emitting diodes (LEDs) that are placed in the optical detector which in turn locates the pointer by detecting the light reflected by it. Prior to registration, the pointer must be calibrated by placing its end in the center of a reference point or antenna located in the Mayfield clamp with which the patient’s skull is fixed. The spatial coordinates of each reference site are paired with the 3D reconstructions of the imaging studies and in this way a brain map is constructed that allows the doctor to visualize in the computer the internal structures of the skull while performing the surgery. To facilitate this procedure, individual reference frames or fiducial markers can be used that stick to the surface of the skull and also contain reflecting spheres of light. These fiducial markers are placed before taking the brain images, which improves the accuracy in the pairing of the imaging information with the spatial information. The surgical material and the microscope are also registered, all of which have adapters with reflecting spheres to achieve their location and detection through the optical detection system. When fiducial markers are not available, superficial anatomical structures of the face and skull, such as the tip of the nose, the earlobe, and the inner canthus of the eye can be used to perform the registration.

Update of intraoperative data in real time

One limitation of neuronavigation is its strict dependence on the accuracy of the registration of the reference points and their correlation with the brain images. The displacement of a reference site or the change of position of the cerebral structures imposed by the dissection of the nervous tissue on the way to the target lesion can alter the accuracy of the neuronavigation system. For this reason, different transoperative imaging techniques can be used to update the structural data of the brain. In some developed countries, intraoperative NMRI images are performed, however, this technology requires a sophisticated infrastructure and an economic investment not available in most hospital centers. The third-dimensional ultrasound has also been used to assess brain displacement during surgery,
showing its usefulness in different clinical studies. However, it has the disadvantage of a lower definition of intracranial tissues and susceptibility to artifacts such as air and sound.\textsuperscript{18,19}

Figure 2 illustrates the complete procedure for performing image-guided neurosurgery, from obtaining preoperative images to recording and updating spatial information in the operating room.

**Figura 1. Procedure for conducting image-guided neurosurgery.**

The first step to perform surgery with a neuronavigation system is to obtain the brain images. To facilitate the subsequent pairing of the imaging data with the spatial information, fiducial markers or reflecting beads can be placed on the patient's skull (A) to serve as reference points and appear in the brain images. The most frequently used studies for this purpose are NMRI and CAT (B), however, functional imaging studies can be performed and these can be superimposed to create a reconstruction in 3D that contains anatomical and functional information (C). Once the brain images are obtained, the spatial information is recorded inside the operating room. For this, the reference frame or antenna and the pointer are used, which indicate the position of the fiducial markers previously placed on the patient's skull (D). The neuronavigation team matches the position of the spatial reference points with the image data allowing to observe in real time the movements of the surgeon on the screen. Sometimes, an update of the image data is required due to the displacement of the brain structures that may occur after the dissection of the nervous tissue and decompression secondary to the craniotomy. In developed countries, this is done through transoperative NMRI studies (E).
Clinical applications of neuronavigation

Neuronavigation has become an essential tool in the treatment of small and deep brain tumors with poorly defined borders and affecting vascular structures of greater importance. Its main advantage is that it shortens the duration of surgery. In addition, a smaller incision is required on the skull, which translates into a lower risk of infection of the surgical wound, a smaller volume of hemorrhage, and a shorter hospitalization time. In the case of the treatment of brain tumors, it has been observed that its use is of special relevance for the approach and delimitation of the surgical edges in cases of low-grade gliomas, in which it is complicated to define the boundaries between the tumor tissue and normal neural tissue. This is enhanced by the use of preoperative functional imaging techniques. The growing evidence of the relationship between the volume of resection, mortality, and risk of recurrence makes neuronavigation a tool that has a direct impact on the prognosis of patients with brain tumors. However, special care must be taken in the technique because, as mentioned before, intracerebral lesions can deform the nervous tissue locally or the surgeon can move the brain during surgery, which alters the calculations made by the navigation system, so that transoperative images are required to update the data and thus improve the accuracy of the procedure. In addition, in cases of rapidly growing tumors, preoperative images should be taken immediately before performing surgery because, if they are taken too early, inaccuracies and greater difficulty may arise in the correlation of spatial information with image reconstruction.

In addition to the resection of intracranial tumors, neuronavigation has applications in the treatment of different neurological diseases and its accuracy seems to be greater in surgery at the base of the skull because the bony structures are practically immobile. In this way, its use is related to better results in the resection of pituitary tumors since it allows a planning of the surgical approach in greater detail through different bony structures such as the trans-sphenoidal route. Additionally, it allows performing intracerebral biopsies, intracranial endoscopy, and functional neurosurgery with greater accuracy than other conventional techniques thanks to the ability to integrate functional imaging techniques information to achieve the minimum risk of damage to eloquent regions and subcortical tracts. Finally, the use of neuronavigation has, in recent years, grown to address spinal diseases requiring spinal surgery.
Disadvantages

Like all medical intervention, neuronavigation also has some difficulties because it takes a long time to record the reference points and calculations to build the brain map, as well as a surgical field limited in space and visibility. In addition, as already mentioned, intracerebral lesions can deform the nervous tissue locally or the surgeon can move the brain during surgery, which alters the calculations made by the navigation system.¹⁵

A further disadvantage of neuronavigation equipment employing optical ultraviolet light detectors is that the space between the detector and the reference points should be free of obstructions, which is not always possible within the context of a common operating theater. For this reason, there are other devices equipped with magnetic field detectors but their availability is lower.³²

Perhaps the greatest limitation of neuronavigation is the high cost and poor infrastructure of many hospital centers in underdeveloped countries, a fact that must be overcome as clinical studies appear in the literature highlighting its cost-effectiveness and as more specialized centers from first world countries share their experience and technical specifications for the performance of image-guided brain surgeries. In spite of this, hundreds of image-guided neurosurgeries are performed every day around the world given the extensive experience of many treatment centers, which places this tool as an example of the benefit of technological development in health care and that it will undoubtedly be improved as new scientific advances arise in the area of biomedical engineering and imaging techniques.

Finally, it is important to mention that the use of neuronavigation in the teaching of neurosurgery can lead to abuse of its use, limiting the development of surgical skills and the acquisition of anatomical knowledge among new neurosurgeons, so it must be remembered that the only role of this type of technology is to act as a support tool and that its absence should not limit the surgical capacity of the surgeon.
Conclusions

Neuronavigation is a novel technology for conducting image-guided surgeries in which the neurosurgeon can observe in real time the situation of surgical instruments as well as each of the maneuvers superimposed on three-dimensional reconstructions of brain images projected on a computer monitor. Its clinical application has been of special importance in the treatment of intracranial tumors and other neurological diseases potentially treatable by surgery. Knowledge of this technique, of its advantages and disadvantages, can improve the prognosis of many patients eligible for this procedure which will continue to be subject to technical improvements as new scientific advances in the area of biomedical engineering and imaging techniques arise. Although it is not a technology that has been developed recently, its use is still limited to first world countries. However, the increase in its availability in underdeveloped countries could benefit hundreds of patients with lesions difficult to approach and should motivate clinical studies to demonstrate its advantages and cost-effectiveness in the treatment of different neurological diseases.

Acknowledgments

To Karina López López, Ariana García Carranza, and Diana Laura Ortíz Vázquez of the Communication Department at the Center Specialized in Neurosurgery and Neurosciences Mexico (CENNM), for their contributions in the illustration and design of the graphics contents of this manuscript.

Conflicts of interest

The authors declare that there are no potential conflicts of interest to report regarding this scientific report.

Funding sources

The authors have not declared any source of funding for this scientific report.
References

Dystonia: Etiology, phenomenology, classification, and treatment of Dystonia

Etiología, fenomenología, clasificación y tratamiento de la distonía

Abstract

In the last 30 years not only have significant progress in the genetic and physiological aspects of dystonia but the diagnostic, classification and treatment approach. For years, oral medications were used exclusively, with the introduction of botulinum toxin and deep brain stimulation, in addition to advances in the understanding of the disease, it has had a positive impact on the quality of life of those who suffer from it and their families. In this article, we will carry out an integral update of the dystonia from its definition, phenomenology, classification, etiology, and treatment.

Resumen

En los últimos 30 años no solo se han logrado avances importantes en los aspectos genéticos y fisiológicos de la distonía sino en el abordaje diagnóstico, clasificación y en el tratamiento. Durante años se utilizaron exclusivamente medicamentos orales, con la introducción de la toxina botulínica y la estimulación cerebral profunda, sumado a los avances en el entendimiento de la enfermedad, se ha logrado impactar positivamente en la calidad de vida de quienes la padecen y sus familias. En este artículo realizaremos una actualización integral de la distonía desde su definición, fenomenología, clasificación, etiología y tratamiento.
**Introducción**

Dystonia is a hyperkinetic movement disorder that causes sustained or intermittent muscle contractions that produce repetitive movements, abnormal postures, or both.¹

The prevalence and incidence of dystonia have been variable in different regions reflecting the different biological substrates of the disease, but this variability may also be related to the different methodological approaches of the studies. A meta-analysis by Steeves et al. estimates that the prevalence of primary dystonia is 16.43 per 100,000 inhabitants (95% CI 12.09-22.32). It is possible, however, that the diagnosis is underestimated. In the same study, they calculated a prevalence per 100,000 inhabitants of 15.4 (95% CI 12.1-19.5) for focal and segmental dystonia, 5.0 (95% CI 3.6-6.9) for cervical dystonia, and 4.2 (95% CI 2.9-6.2) for blepharospasm.² In Latin America, there are few epidemiological data on the prevalence of dystonia.³,⁴ Dystonia can also be associated with non-motor symptoms in up to 70% of cases.⁵ In this article we will review the definition, phenomenology, classification, diagnosis, and treatment.

1. Definition

This disease was first described by Schwalbe in 1908 when he published his thesis on a family with three affected children suffering from generalized primary dystonia. Three years later, Oppenheim described the same disorder in four patients and coined the word “dystonia” calling this syndrome “deforming muscular dystonia” or “progressive lordotic dysbasia.”⁶ Then, in 1975, David Marsden described dystonia as a disorder of organic origin, which also includes blepharospasm, spasmodic torticollis, and writer’s cramp.⁷,⁸ In 1984, Stanley Fahn proposed the first definition of dystonia as sustained muscular contractions that frequently cause torsion and repetitive movements or abnormal postures.⁹,¹⁰

This definition of dystonia remained in effect for more than 25 years. Since it did not comprehensively consider all aspects of dystonia, however, a consensus of experts got together in 2012 to develop a new definition. This classification was published in 2013 by the Movement Disorders Society, and defines the disease as follows: “Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned and twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.”¹¹ The word dystonia has been used to describe not only the motor phenomenology but also a clinical syndrome and now it is recognized as a disease that may be genetic, sporadic, but may also be secondary to other diseases such as Wilson’s disease, immune encephalopathy, neuroferritinopathy, and cerebral palsy among others.¹²

2. Phenomenology

A fundamental characteristic that differentiates dystonia from other hyperkinetic movement disorders is its predictability and the pattern nature of muscle contractions. Dystonic postures can flex, extend, or twist a part of the body along its main axis. In axial dystonia, scoliosis and camptocormia are often observed. Dystonic postures can cause pain, especially cervical dystonia.¹³ Dystonic movements have a torsional nature and usually a direction, they are repetitive, predictable and have a peak in which the movement is sustained and the direction is maintained for an instant. An example of this is cervical dystonia, in which the movements of the neck have a directional preponderance causing an abnormal position resulting in postures such as laterocollis (lateral tilt), retrocollis (backward tilt), torticollis (horizontal rotation), or anterocollis (anterior tilt). Other types of postures secondary to dystonic movements are ulnar deviation, plantar flexion, vocal fold adduction, and eye closure.¹⁴

The speed and rhythmicity of the movements can be variable. Though they are usually arrhythmic, they can also be rhythmic, this type of movement has been called dystonic tremor. Dystonia can be
difficult to differentiate from other movement disorders such as essential tremor, for it is necessary to take into account its directional character and the worsening of the amplitude of the tremor when the movement goes in the opposite direction to dystonia. Dystonic movements can be differentiated from other movement disorders such as chorea, in which the movements are unpredictable, follow a flow from proximal to distal, and are usually associated with loss of tone. It is also possible to differentiate dystonia from tics because in the former there is no urgency to perform the movement and there is no relief after executing it. Other features that support the diagnosis of dystonia have been described such as mirror dystonia, in which, while performing a motor task with one extremity, similar movements are observed but with dystonic characteristics in the contralateral limb. There is also action dystonia or task-specific dystonia, where dystonia is activated or increased in intensity by a voluntary task. Dystonic movements can be attenuated by voluntary movements called antagonistic gestures or sensory trick phenomenon. The presence of these phenomena supports the diagnosis of dystonia. In some patients, simply thinking about the trick helps improve dystonia.

3. Classification
The current classification of dystonia divides it into two main axes: Axis 1 - Clinical Characteristics; Axis 2 - Etiology.

In axis 1, age at onset, body distribution, temporal pattern, and additional movement disorders or neurological features are included. The age at onset is subdivided into five groups, onset in infancy (from birth or lactation to 2 years), childhood (3-12 years), adolescence (13-20 years), early adulthood (21-40 years), and late adulthood (>40 years). In reference to body distribution, it is called focal dystonia when only one region is affected, it is segmental when two or more contiguous regions are affected, multifocal if two or more non-contiguous regions are affected, hemidystonia when it is limited to half the body, and generalized when it affects the trunk and at least two affected regions. The temporal pattern includes the disease course (static or progressive) and the variability of the symptoms (persistent, fluctuating, specific, and paroxysmal). Finally, it must be established whether dystonia is associated with other movement disorders.

In axis 2, dystonia is classified according to the etiology in nervous system pathology (degeneration, structural lesion or absence of both) and in hereditary or acquired causes (perinatal injury, infection, drugs, toxic, vascular, brain damage). Table 1 summarizes the characteristics of axis 1, while Table 2 shows the components of axis 2. It is also important to perform the differential diagnosis with other entities that may be similar or mimic dystonia.

4. Pathophysiology
The pathophysiology of dystonia is complex and involves multiple systems at the central and peripheral levels, as well as affecting different circuits in the basal ganglia, thalamus, cerebellum, and cortex: all of them involved in motor control and the inhibition of unwanted involuntary movements. However, in practical and simplified terms, the following main alterations are described:

a. Loss of inhibition
The nervous system is composed of excitatory and inhibitory circuits in equilibrium with each other. In dystonia, it seems that the inhibition is defective, which leads to loss of selectivity and excess of movement. For the construction of a motor act, there must be an excitatory signal for the desired movement and an inhibiting command for the unwanted movements. This occurs in the basal ganglia circuit through the direct and indirect pathways, respectively. Additionally, there is also an inhibitory control called “surround inhibition” at the cortical level, which blocks the excitation of neuronal groups not required for the execution of a motor act. The loss of inhibition has also been
Table 1. Axis 1: Classification of dystonia according to clinical characteristics.

<table>
<thead>
<tr>
<th>Age of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation &lt;2 years of age</td>
</tr>
<tr>
<td>Presentation 3-12 years of age</td>
</tr>
<tr>
<td>Presentation 13-20 years of age</td>
</tr>
<tr>
<td>Presentation 21-40 years of age</td>
</tr>
<tr>
<td>Presentation &gt;40 years of age</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>One affected body region</td>
</tr>
<tr>
<td>Two contiguous body regions</td>
</tr>
<tr>
<td>More than two non-continuous regions</td>
</tr>
<tr>
<td>Trunk and at least two affected regions</td>
</tr>
<tr>
<td>An affected hemibody</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Temporal pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Course of the disease</td>
</tr>
<tr>
<td>Variability of symptoms</td>
</tr>
<tr>
<td>Diurnal fluctuations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coexistence of other neurological disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonism, myoclonias.</td>
</tr>
<tr>
<td>Dystonia alone or in combination with other movement disorders.</td>
</tr>
</tbody>
</table>

Table 2. Axis 2: Classification of dystonia according to etiology.

<table>
<thead>
<tr>
<th>Central nervous system disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathology of the nervous system</td>
</tr>
<tr>
<td>Structural lesion</td>
</tr>
<tr>
<td>No evidence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inherited or acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal dominant, autosomal recessive, X-linked, mitochondrial.</td>
</tr>
<tr>
<td>Perinatal injury, infection, drugs, toxic, vascular, neoplasms, brain tumor, psychogenic.</td>
</tr>
<tr>
<td>Sporadic or familial.</td>
</tr>
</tbody>
</table>

studied in more basic levels of motor control, such as at the medullary level. It was precisely in the medulla and brainstem where it was demonstrated for the first time. Some examples are loss of reciprocal inhibition in the forearm muscles of patients with focal hand dystonia as well as abnormalities opening and closing the eyelids due to loss of reciprocal inhibition and decreased inhibition of the blinking reflex seen in blepharospasm. This loss of reciprocal inhibition may be partly responsible for the antagonistic muscle co-contraction that characterizes dystonia.  

b. Sensory Alterations and in Sensory-Motor Integration

The sensory trick phenomenon is clear proof of the importance of perception in the expression of the disease, however, it is not yet understood. In some experiments the vibration of the affected arm can induce dystonia in patients with focal
dystonia of the hand; this can be blocked with diluted lidocaine, which may indicate that this phenomenon is mediated by afferent fibers from the neuromuscular spindle. Sensory abnormalities have been observed, such as alterations in spatial localization and temporal discrimination, present in both hands of patients with focal dystonia of the hand and even in the hands of patients with blepharospasm and cervical dystonia.

c. Abnormal Brain Plasticity
There is evidence in animal studies that suggest that neuronal plasticity is a key factor in the pathophysiology of dystonia. Long-term potentiation and depression models are typical models of plasticity in mammals and there is ample evidence that loss in this synaptic homeostasis is the cause of motor disorder. It has been postulated that the synchronous and repetitive activity can produce afferences to the motor and sensitive area that produce a “bad adaptation” in the cortical plasticity. This has been observed in animal and human models in which abnormal remodeling of the primary somatosensory cortex occurs. This excess of neuronal plasticity, together with the lack of factors that model the synaptic potentiation in cortico-striatal circuits, generates a tendency to form associations between sensory inputs and motor outputs that prevent a differentiation of the motor programs. During learning tasks, a fine regulation usually occurs that reduces interference between superimposed motor tasks by avoiding the combination of unwanted movements. This lack of inhibition and loss of homeostasis in brain plasticity can lead to the consolidation of abnormal motor engrams that contain redundant information causing the motor overflow that produces the typical dystonic phenomena.

5. Etiology of Dystonia
Although most patients with dystonia are classified as sporadic, genetic factors are central to the development of isolated and combined primary dystonias. There are dystonias with autosomal dominant inheritance, however, some of them with low penetrance; therefore, not all carriers of the mutation will present the phenotype although they can potentially transmit it to their offspring. Dystonia may also be inherited in an autosomal recessive or X-linked manner.

The most frequent isolated generalized dystonias are related to the genes DYT1, DYT4, and DYT6, being inherited in an autosomal dominant manner with incomplete penetrance secondary to mutations in TORIA, TUBA4, and THAP1, respectively. Mutations in DYT5a and b (GCH1 and TH), DYT3, DYT12, and DYT16 can be accompanied by parkinsonism whereas DYT11 (SGCE) and DYT15 by myoclonias. Table 3 summarizes some of the hereditary dystonias including the function of the encoded protein, its phenotype, and year of its description. Additionally, the autosomal recessive mutations of PARKIN and DJ1 seen in early-onset Parkinson’s disease may also be accompanied by limb dystonia. It is important to note that in mutations that cause generalized dystonia such as DYT1, DYT4, and DYT6, in addition to reduced penetrance there is variable expressibility, so in some cases, the clinical expression can also be focal.

Genes associated with craniocervical dystonia have been recently described. The first new gene described was CIZ1 (DYT23) (Cip1- Interacting zinc finger protein 1). This mutation has been reported in adult-onset cervical dystonia. Mutations in ANO3 (DYT24) (Anoctamin 3) have been reported in predominantly craniocervical dystonia, with a wide age range of onset. ANO3 encodes a transmembrane protein that binds to calcium channels activated by calcium and that play an important role in transduction.

Heterozygous mutations in the GNAL (DYT25) gene (Guanine nucleotide-binding protein subunit alpha L), which codes for the alpha subunit of the Golf protein, causes cervical dystonia. The Golf protein has been found coupled to dopamine D1 and adenosine A2A receptors. These mutations have high penetrance but not complete. Other genes related to cervical skull dystonia are: DYT 7, DYT 17, DYT 26, and DYT 27.

In order to perform a phenotypic and genetic
Table 3. Hereditary dystonia, coded protein function, phenotype, and year of description.

<table>
<thead>
<tr>
<th>Dystonia Type</th>
<th>Phenotype</th>
<th>Protein Function</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYT-TOR1A (DYT1)</td>
<td>Generalized dystonia of early onset, usually starts in the lower limbs.</td>
<td>Located in the endoplasmic reticulum, ATPase associated with several cellular functions, could be considered to be a chaperone.</td>
<td>1997</td>
</tr>
<tr>
<td>DYT-THAP1 (DYT6)</td>
<td>Dystonia with onset in adolescence with mixed phenotype, cranial-cervical involvement.</td>
<td>Transcription factor. Regulates the expression of TOR1A.</td>
<td>2009</td>
</tr>
<tr>
<td>DYT-GNAL (DYT25)</td>
<td>Dystonia of adult onset, segmental, predominantly cranial and cervical.</td>
<td>Protein involved in transduction. Encodes for the alpha subunit of the Golf protein, which is coupled to D1 and A2A receptors.</td>
<td>2013</td>
</tr>
<tr>
<td>DYT-ANO3 (DYT24)</td>
<td>Late-onset craniocervical dystonia.</td>
<td>Transmembrane protein that binds to calcium channels activated by calcium, playing an important role in transduction.</td>
<td>2012</td>
</tr>
<tr>
<td>DYT-CIZ1 (DYT23)</td>
<td>Cranio-cervical dystonia.</td>
<td>Protein 1 interaction with zinc fingers.</td>
<td>2012</td>
</tr>
<tr>
<td>DYT-GCH1 (DYT5a)</td>
<td>Dystonia that responds to dopa. Typically with daytime fluctuation. Starts in lower limbs.</td>
<td>Enzyme involved in the synthesis of tetrahydrobiopterin.</td>
<td>1995</td>
</tr>
<tr>
<td>DYT-PRKRA (DYT16)</td>
<td>Dystonia-Parkinsonism.</td>
<td>Protein kinase with function in response to cellular stress.</td>
<td>2008</td>
</tr>
</tbody>
</table>

approach, we studied dystonia according to whether it occurs in isolation, combined with myoclonus or Parkinsonism, or in a paroxysmal manner. Figure 1 shows the diagnostic approach through the phenotype. Additionally, it should be considered if the dystonia involves muscles in the cranial and cervical region, in the larynx, if it is generalized, focal, or multifocal, in order to perform an even more precise orientation. Figure 2 and Figure 3 show an approximation according to these more specific clinical characteristics of dystonia to guide and facilitate the genetic search.

6. Non-motor characteristics of Dystonia
Clinical observation has allowed recognizing the coexistence of depression and anxiety in patients with dystonia. The prevalence of these disorders varies; however, it is estimated between 12 and 71% though most studies show a range between 25 and 50%, a similar percentage to patients with Parkinson’s disease. In both cases, this frequency is higher than in healthy individuals and other medical conditions. There are controversy and little knowledge about whether the neuro-psychiatric symptoms are a consequence of the neurobiology of dystonia or if they are a secondary expression in coping with the severity of the disease. There is more evidence in favor of the fact that the alterations of affect are secondary to the alteration of the circuits involved in dystonia. In a study of 89 patients with focal dystonia, 57.3% had psychiatric disorders compared to 24% of healthy subjects and 34.6% of patients with hemifacial spasm. In another study carried out in Germany, a prevalence of 70.3% was reported for psychiatric or personality disorders, with those in the anxious
spectrum being the most frequent. Functional studies of dopamine transporters, as well as ligands of D2/D3 receptors, suggest a role of dopamine in the pathophysiology of depression in patients with cervical dystonia. Another study compared the frequency of psychiatric symptoms in the initial evaluation with another subsequent evaluation at five years. It was reported that the prevalence was similar and that the symptoms did not change over time. In comparison, the motor evaluations presented improvement; this suggests that the presence of psychiatric symptoms are independent of the severity of motor symptoms. For all the above, it is considered that neuro-psychiatric symptoms may be related to a process underlying the pathophysiology of dystonia. It is possible that elements of reactive depression triggered by a visible, disabling, and potentially painful disease may exacerbate affective symptoms like anxiety and depression, however, these aspects have a profound impact on the quality of life.

In this regard, a study conducted in 50 Dutch patients with dystonia reported worse scores on the quality of life scale compared with patients diagnosed with a psychiatric illness. Additionally, the most important predictors of quality of life were the severity of their depression and pain, not the motor symptoms. Finally, some alterations in cognition have also been described, especially in executive functions such as mental flexibility, attentional deficits, and verbal fluency, among others.

7. Treatment
In the last 25 years not only has it been possible to delve into the molecular aspects of dystonia, but at the same time, the therapeutic options have changed drastically. For decades, oral medications were used exclusively, though they had a limited benefit and important adverse effects. With the introduction of botulinum toxin application for the treatment of focal dystonias, and later with the advent of deep brain stimulation (DBS) surgery, the therapeutic approach of these entities has been modified, which in turn has improved the quality of life of the patients.
**Figure 2.** Genetic diagnosis approach according to the clinical characteristics of Dystonia (Isolated).

**Figure 3.** Genetic diagnosis approach according to the clinical characteristics of Dystonia (Combined).
Oral Medications
The efficacy of high-dose trihexyphenidyl for the treatment of generalized primary dystonia was established in a prospective, double-blind study by Burke et al. in 1986. Since then, few oral medications have been successful in the treatment of dystonia. Oral pharmacological treatment has not changed much over the years, currently, anticholinergics (especially trihexyphenidyl) and baclofen are used in addition to benzodiazepines and levodopa.

Levodopa for the treatment of dystonia that responds to dopa (DYT5) has allowed demonstrating a significant benefit in this group of patients. Tetrabenazine and clozapine can be used for secondary dystonia and metabolic syndromes such as glutaric acidemia, among others.

Intrathecal infusion of baclofen
The intrathecal infusion of baclofen has also been used for the treatment of generalized dystonia refractory to oral medications. However, it has been shown to be more beneficial in patients with dystonia associated with spasticity or pain.

Botulinum toxin
The treatment of focal dystonia, previously limited to oral medications, has been transformed by the introduction of botulinum toxin. Since the 1980s, the application of botulinum toxin has become a first-line treatment for the various forms of focal dystonia. This treatment is used locally, having high efficacy and causing minimal side effects. Table 4 summarizes the recommendations of the American Association of Neurology for the use of botulinum toxin in different locations of dystonia and spasticity. The toxin blocks the vesicular release of acetylcholine at the neuromuscular junction, causing temporary local chemo-denervation and muscle weakness, reducing excessive dystonic muscle activity.

Botulinum toxin is a protein extracted from the bacterium Clostridium botulinum of which eight different antigenic variants are currently known (denominated from A to G), which share similar structural characteristics. Out of those toxins, type A and type B toxins are currently in use (OnabotulinumtoxinA-Botox, AbobotulinumtoxinA - Dysport, IncobotulinumtoxinA - Xeomin, RimabotulinumtoxinB - Myobloc). The toxin consists of a light and heavy chain linked by a disulfide bond. The light chain acts on different proteins according to the toxin subtype. The light chain of toxin A acts on the protein SNAP-25 (associated with the synaptosome), which is necessary for the fusion of the vesicle with the presynaptic membrane.

Botulinum toxin penetrates into the presynaptic terminal of the neuromuscular junction by binding the heavy chain to a specific receptor of the plasma membrane to be captured by endocytosis. Botulinum toxin is a protein that is foreign to the immune system, therefore neutralizing antibodies can be produced to block its effect. The risk for these antibodies to be generated is application at short intervals, usually less than three months, and high total doses. Clinically, this resistance can be suspected when the patient does not show improvement and does not develop weakness or atrophy in the injected muscles.

Deep brain stimulation (DBS)
In the mid-20th century, the surgical treatment of generalized dystonia consisted of surgical lesions, classically thalamic. Thalamotomy provided significant benefit for dystonia in some patients; however, it frequently caused permanent disabling neurological effects. After observing that pallidotomy in patients with Parkinson's disease improved dyskinesias, interest in the globus pallidus was aroused as a surgical target in dystonia. After the introduction of DBS for the treatment of essential tremor and Parkinson's disease in the mid-1990s, this therapy was established as an alternative to ablative procedures for the treatment of movement disorders. Parallel bilateral stimulation began to be used for the treatment of generalized dystonia about a decade ago.

In patients with primary generalized dystonia, especially those with dystonia DYT1, the response is dramatic. Studies of bilateral DBS of the internal globus pallidus (Gpi) for the treatment of
primary dystonia show a significant reduction of 50-80% in dystonic symptoms\textsuperscript{54-56} and a significant improvement in function and quality of life.\textsuperscript{56,57}

This therapeutic strategy has also become a crucial treatment option for patients with primary generalized dystonia refractory to pharmacological management. In addition, long-term follow-up studies have reported sustained clinical improvement in patients with follow-ups at 5 and 10 years.\textsuperscript{55-59} However, there are some considerations for the selection of patients, on whom the success of the procedure depends.\textsuperscript{54,60}

It is considered that there are a few good outcome predictors for DBS, among which are a lower severity, early age at the time of surgery, carrying a DYT1 mutation, shorter disease duration, and absence of fixed skeletal deformities. Regarding the duration of symptoms, there is controversy in the literature. An observational study found that the duration of symptoms rather than age at the time of surgery was inversely correlated with the outcome. Skeletal deformities were generally associated with worse outcomes. Therefore, it is considered that age should not be used as inclusion or exclusion criteria for Gpi DBS, as both children and adults can benefit from the procedure.\textsuperscript{54,60}

The use of DBS for the treatment of generalized primary dystonia, especially DYT1 has been widely accepted. There are questions about its effectiveness in secondary forms. The data regarding the efficacy of deep brain stimulation for secondary dystonia in the reports of individual cases or small series of cases with different forms of secondary dystonia range from no benefit to dramatic improvement. Cases with good response have been reported as dystonia due to hereditary-degenerative diseases such as PKAN (Pantothenate kinase-associated neurodegeneration) and Lubag Syndrome (X-linked dystonia-parkinsonism).\textsuperscript{64,65}

The detection of psychiatric comorbidity, including depression and suicide attempts, is important in the preoperative evaluation. If psychiatric symptoms are considered serious this may be a contraindication for surgery. Comorbidities such as hypertension and cognitive deterioration should be taken into account when analyzing risks and benefits. Careful evaluation of other neurological disorders should be included in the evaluation, especially in cases of secondary dystonia.\textsuperscript{63} It is important to emphasize that pharmacological

---

Table 4. Level of recommendation of the American Association of Neurology for the use of botulinum toxin in different sites for dystonia and spasticity.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Onabotulinum</th>
<th>Incobotulinum</th>
<th>Abobotulinum</th>
<th>Rimabotulinum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Type A</td>
<td>Type A</td>
<td>Type B</td>
<td>Type B</td>
</tr>
<tr>
<td>Blepharospasm</td>
<td>Level B</td>
<td>Level B</td>
<td>Level C</td>
<td>Level U</td>
</tr>
<tr>
<td>Cervical dystonia</td>
<td>Level B</td>
<td>Level B</td>
<td>Level A</td>
<td>Level A</td>
</tr>
<tr>
<td>Upper limb spasticity</td>
<td>Level A</td>
<td>Level A</td>
<td>Level A</td>
<td>Level B</td>
</tr>
<tr>
<td>Lower limb spasticity</td>
<td>Level A</td>
<td>Level U</td>
<td>Level A</td>
<td>Level U</td>
</tr>
</tbody>
</table>

**Level A**: effective recommendation means that the intervention should be offered.

**Level B**: probably effective recommendation means that the intervention should be considered.

**Level C**: possibly effective recommendation means that the intervention could be considered.

**Level U**: insufficient recommendation evidence means that there is no evidence to support or refute the effectiveness of the intervention.
Conclusions

Dystonia today constitutes a fundamental field of study in the hyperkinetic movement disorders through which we can approach the understanding of the functioning and integrity of the motor systems at the level of the basal ganglia, cerebral cortex, and cerebellum. Its recognition and adequate classification allow a better diagnostic and genetic approach, making it easier to choose the most appropriate pharmacological, therapeutic, or surgical intervention which will impact the patient’s quality of life.

Conflicts of interest

We declare that this research has no conflicts of interest.

Funding

No funding was received for the realization of this work.
References

Case report

Remote cerebellar hemorrhage after thrombolysis

Hematoma remoto cerebeloso post-fibrinolisis

Abstract

Introduction: Intracerebral haemorrhage after intravenous thrombolysis is a relevant complication of ischaemic stroke. Its mechanisms are not well known; making a distinction between haemorrhagic transformation of the ischemic region and hematomas unrelated to that area, referred to as remote intracerebral haemorrhage (rICH).

Case report: An 84-year-old male, independent in all activities of daily living with hypertension as a cardiovascular risk factor suffers abruptly from aphasia and right faciobrachial hemiparesis. Cerebral Computed Tomography (CT) does not show any findings of bleeding or acute ischemia. Intravenous thrombolysis is administrated in the absence of contraindication. After 24 hours, control CT showed a parenchymatous haemorrhage in the right cerebellar amygdala and no signs of haemorrhagic transformation of the infarct. Follow-up Magnetic Resonance imaging showed the absorption of the cerebellar hematoma, without signs of previous ischemia in that location.

Conclusion: rICH is not an uncommon post-thrombolytic complication and its long-term morbidity and mortality is considerable. The finding would force us to think about small vessel disease with hypertensive microangiopathy as one of the main predisposing factors of cerebellar rICH, in contrast with lobar rICH, more related with leucoaraiosis, amyloid angiopathy and microbleeds.
Resumen

Introducción: La hemorragia intracraneal tras fibrinolisis intravenosa es una de las complicaciones más trascendentes del ictus isquémico. Sus mecanismos precursores aún no son bien conocidos, diferenciando la transformación hemorrágica del área isquémica y los hematomas no relacionados con dicha región, conocidos como hemorragias intracraneales remotas (HICr).

Reporte de caso: Varón de 84 años, independiente en sus actividades diarias e hipertenso. De forma brusca sufre afasia y hemiparesia facio-braquial derecha. En Tomografía Computarizada cerebral no se observan signos de sangrado ni hallazgos isquémicos agudos. Al no existir contraindicación se realiza fibrinolisis intravenosa, observándose en el control tomográfico a las 24 horas una hemorragia parenquimatosa en amígdala cerebelosa derecha, sin transformación hemorrágica del área de infarto. En la Resonancia Magnética de seguimiento se aprecia reabsorción del hematoma cerebeloso sin signos de isquemia previa en dicha localización.

Conclusión: Los HICr no son una complicación tan infrecuente de la terapia fibrinolítica y su morbimortalidad a largo plazo no es despreciable. Su hallazgo en pruebas de imagen nos obligaría a pensar en patología de pequeño vaso, destacando la microangiopatía hipertensiva como uno de los principales factores predisponentes de HICr cerebelosos; a diferencia de las HICr lobares, en las que la leucoaraiosis, la angiopatía amiloide y los fenómenos de microsangrado estarían más asociados.

Palabras clave

Corresponding author:
Álvaro Lambea Gil.
Phone: +34 677116926.
E-mail: alvarolambea@gmail.com
Introduction

Intracranial hemorrhage after intravenous thrombolytic therapy is one of the most clinically relevant complications in the management of ischemic stroke. However, its pathophysiological foundations are still not well known.

In the evaluation of the precursor mechanisms of intraparenchymal brain hemorrhage post-thrombolysis, a distinction has been made between bleeds over areas of cerebral ischemia where revascularization has been tried (ICH) compared to those on regions unrelated to the ischemia causing the initial symptoms, known as remote intracranial hemorrhages (RICH). The latter, less addressed in the literature, carry a higher risk of long-term morbidity and mortality. They may appear isolated or associated with an ICH in patients undergoing thrombolysis, which is between 1.3 and 3.7% of the total number of patients with ischemic stroke.

We present the case of a patient with acute ischemic stroke who, after receiving intravenous thrombolytic therapy, suffered a cerebellar hemorrhage not topographically related to the initial clinical presentation.

Clinical case

An 84-year-old male, functionally autonomous (score 0 in the mRS), with arterial hypertension as the only known cardiovascular risk factor and with no antiplatelet or anticoagulant treatments suffered an abrupt mixed aphasia with motor predominance and mild right faciobrachial hemiparesis scoring 9 in the NIHSS. A simple cerebral computed tomography (CT) shows moderate leukoaraiosis data with no signs of bleeding or acute ischemic findings and a score of 10 on the ASPECT scale. The picture is compatible with a partial anterior circulation infarct (PACI) dependent on a distal segment of the left middle cerebral artery (Figure 1A and 1B). As there was no contraindication, an intravenous thrombolysis was performed at 2h 30min from the beginning of the clinical examination. He was admitted to the stroke unit without clear clinical improvement, maintaining blood pressure values below 180/105 mmHg and with no relevant pathological findings in biochemistry, blood count, or coagulation. In the tomographic control at 24-hours post-thrombolysis, a parenchymal hemorrhage was observed in the right cerebellar amygdala, without hemorrhagic transformation of the infarction area in the left frontal lobe (Figure 2A and 2B).

In the follow-up brain magnetic resonance imaging (MRI), resorption of the cerebellar hemorrhage without signs of previous infarction was observed (Figure 3). Diffuse leukoaraiosis is confirmed in turn with a Fazekas grade 2.

Discussion

Unlike ICHs which are associated with cardioembolic pathology or occlusion of large intracerebral arteries, RICHs seem to have a small vessel disease as a predisposing factor. Alteplase (recombinant tissue Plasminogen Activator r-tPA) would thus act on areas more prone to disruption of the blood-brain barrier, without being able to rule out a possible interaction with undiagnosed base coagulopathies.

Despite discrepancies between some studies, the factors related to small vessel pathology and frequently associated with RICH are leukoaraiosis, amyloid angiopathy, and micro-bleeding phenomena. These hemorrhages are more prevalent in women and patients of more advanced age. According to the latest published series, these factors seem to predispose concretely to lobar RICHs, whereas deep, brainstem, and cerebellar RICHs would be related to hypertensive angiopathy in accordance with the case presented here. However, it could not be ruled out that some of these RICHs were actually ICHs on ischemic areas not visible by the CT brain scan performed at admission.

Our clinical case shows an atypical location of a remote hemorrhage. This location (cerebellar...
Case report
Remote cerebellar hemorrhage post-thrombolysis

Figure 1. Initial simple brain CT pre-thrombolysis: supratentorial (A) and infratentorial (B) cut. The supratentorial section shows diffuse periventricular hypodense areas in the context of leukoaraiosis.

Figure 2. Simple brain CT of post-thrombolysis control at 24 hours: supratentorial section (A), where a hypodense area compatible with ischemic stroke is observed (arrow); and infratentorial (B), showing hyperdense area suggestive of hemorrhage in right cerebellar tonsil.
Remote cerebellar hemorrhage post-thrombolysis

As already explained, hypertensive microangiopathy would be one of the most plausible predisposing factors. This is unlike what occurs in remote cerebellar hemorrhages associated with a neurosurgical intervention, in which the most feasible explanation would be a hemorrhagic venous infarction due to excessive CSF drainage.

This existing association between RICH and small vessel pathology has led some authors to propose pre-thrombolysis MRI. It is a useful imaging technique to help assess the patient’s previous situation, taking into consideration the greater risk of death and functional dependence (70.3%). However, it is not as accessible in hyperacute stroke care and the assessment of aspects such as the number of microbleeds would be impractical for rapid decision making in daily clinical activity when CT is already able to detect leukoaraiosis associated with intraparenchymal bleeding.

Knowing this association and having the possibility to detect it, several works have analyzed the benefit of r-tPA in these patients. For those in whom the existence of microbleeds is already known from previous MRIs, it is not clear that the increase in risk of ICH or RICH completely exceeds the possible benefit of thrombolysis. Regarding the presence of leukoaraiosis, patients who underwent alteplase showed a better functional prognosis at 3-6 months of the event compared to those who did not. Finally, if we assess the benefit of low doses of fibrinolytic compared to standard doses of 0.9 mg/kg in these patients with the aim of reducing the risk of bleeding, a recent study did not show that the reduced dose of 0.6 mg/kg was equivalent in terms of good functional prognosis at 3 months despite being associated with fewer cerebral hemorrhages, therefore, without trials that take into account groups with signs of small vessel pathology, international guidelines continue to recommend standard doses.
Conclusion

In conclusion, remote hemorrhages are not an infrequent complication of thrombolytic therapy and its long-term morbidity and mortality are not negligible. The finding of one of them in imaging tests would force us to think of small vessel pathology, highlighting hypertensive microangiopathy as one of the main predisposing factors of remote cerebellar hemorrhages.

Conflicts of interest
We declare that this research has no conflicts of interest.

Funding
No funding was received for the realization of this work.
References


Estimado académico:

Por medio de la presente, es un gusto saludarle y extenderle la más cordial invitación a colaborar con la publicación de artículos de investigación original, básica, tradicional o aplicada, casos clínicos o artículos de revisión en la Revista Mexicana de Neurociencia, órgano oficial de difusión científica de la Academia Mexicana de Neurología.

La publicación ha sido incluida recientemente en el índice de revistas de CONACyT, y se trabaja para que en breve esté disponible en las plataformas OVID y SciELO, especialmente en PubMed.

Estamos seguros que con su amplia trayectoria académica le permitirá participar e invitar a colaborar a sus distinguidos colegas, que con su participación enriquecerán nuestra revista.

El Comité Editorial está formado por investigadores de diversas instituciones de nuestro país y del extranjero, quienes cuentan con reconocida calidad académica.

Esperamos que usted y cada integrante de la Academia Mexicana de Neurología se sientan parte y sumamente orgullosos de la Revista Mexicana de Neurociencia.

Reciba un cordial saludo.
Atentamente,

Dra. Carolina León
Co-Editor

Dr. Ildefonso Rodríguez
Editor

Dr. Antonio Arauz
Co-Editor

Revista Mexicana de Neurociencia

San francisco 1384 Torre B 7, Col. Del Valle, Ciudad de México, C.P. 03100
Teléfonos: +52 (55) 5559 9833 / +52 (55) 5575 9312
www.neurologia.org.mx www.revmexneuroci.com