REVISTA MÉDICA DEL
HOSPITAL GENERAL
DE MÉXICO

Revista Médica del Hospital General de México is Indexed in: SciELO; Latindex; DOAJ; Scopus; EMBASE/Excerpta Medica; Periódica-Índice de Revistas Latinoamericanas en Ciencias – DGBSDI, UNAM; LILACS; Bibliomex Salud; SIIC/siicsalud; Ulrich's International Directory

Volume 88, Issue 2, April-June 2025 ISSN: 0185-1063 / eISSN: 2524-177X

EDITORIAL

ORIGINAL ARTICLES

REVIEW ARTICLES

CLINICAL CASES

HOSPITAL GENERAL de MÉXICO
DR. EDUARDO LICEAGA

PERMANYER MÉXICO
www.permanyer.com

REVISTA MÉDICA DEL HOSPITAL GENERAL DE MÉXICO

Revista Médica del Hospital General de México is Indexed in: SciELO; Latindex; DOAJ; Scopus; EMBASE/Excerpta Medica; Periódica-Índice de Revistas Latinoamericanas en Ciencias – DGBSDI, UNAM; LILACS; Bibliomex Salud; SIIC/siicsalud; Ulrich's International Directory

10987AMEX252

Revista Médica del
Hospital General de México

PERMANYER

Check for updates

EDITORIAL

Neuropathic pain: from concept to multimodal treatment

José D. Carrillo-Ruiz[1,2], José R. Carrillo-Márquez[3], and Ma. Fernanda Carrillo-Márquez[4]*

[1]Research Direction and Stereotactic, and Functional Neurosurgery Service, Hospital General de México Dr. Eduardo Liceaga, Secretaría de Salud; [2]Coordination of Neurosciences, Faculty of Psychology, Universidad Anáhuac México; [3]School of Medicine, Universidad West Hill; [4]Faculty of Health Sciences, Universidad Anáhuac México. Mexico City, Mexico

Introduction

Pain has been considered one of the main reasons why a patient goes to the doctor, being regarded as one of the most unpleasant experiences: anyone has experienced pain at some point, knowing that it can present itself as something whose intensity can be annoying and tolerable to something that can become completely disabling for daily life. This preface deals with neuropathic pain where the nervous system is the main actor both in its injury and in its reaction, understanding its concept, anatomy, physiology, pathophysiology, classification, and the consequent therapy involved in its resolution.

Concept

Pain is described as an unpleasant sensation and is considered by the WHO as another vital sign to be taken into consideration, so its importance is fundamental, since in a general consultation more than 90% of patients go to the doctor for pain. The International Association for the Study of Pain (IASP) has recently modified its definition by establishing that pain is: "an unpleasant sensory and emotional experience associated with or similar to that associated with an actual or potential tissue injury"[1]. The definition covers a specifically physiological part where there is an injury to the body with an immediate basic neurological response, which is highly objective; but that also encompasses another nervous part involving the limbic circuits on emotions, whose meaning is highly subjective for the patient.

Physiology and pathophysiology

The physiology of pain involves the external or internal stimulation of receptors for this modality, its transmission to the higher centers, its regulation, and later the understanding of it with its immediate response to pain by the individual. Then, four phases are described: (1) transduction: it is the conversion of the external or internal stimulus (mechanical, chemical, or temperature fashion, through any of the receptors, in this case, nociceptive) (2) transmission: it is known as the transfer of the action potential in each fiber of the receptors recruiting in the nerve bundles of the peripheral nerves to the spinal cord (3) modulation: it is the inhibition or excitation of the fibers that enhance the sensation of pain by means of neurotransmitters (4) perception: once the electrical stimulus ascends to the primary sensory cortex, it can be transferred to the cingulate and prefrontal cortex to give it meaning[2] (Fig. 1).

It should be remembered that there are different classifications to understand pain, including its etiology: somatic, neuropathic, psychogenic, or mixed. Neuropathic pain shows clinical characteristics of the injury to the nerve, which corresponds to a burning and scratching pain, sometimes described as "smearing chili," which is paroxysmal, abrupt, and covers a dermatome of an altered nerve[3]. Although it can be acute, the pain becomes subacute or downright chronic (for more than 3 months). The fibers involved in pain transmission correspond to the A-delta fibers for the transmission of acute pain, as the speed is moderately fast,

***Correspondence:**
José D. Carrillo-Ruiz
E-mail: josecarrilloruiz@yahoo.com

Date of reception: 27-01-2025
Date of acceptance: 29-01-2025
DOI: 10.24875/HGMX.M25000050

Available online: 01-04-2025
Rev Med Hosp Gen Mex. 2025;88(2):57-61
www.hospitalgeneral.mx

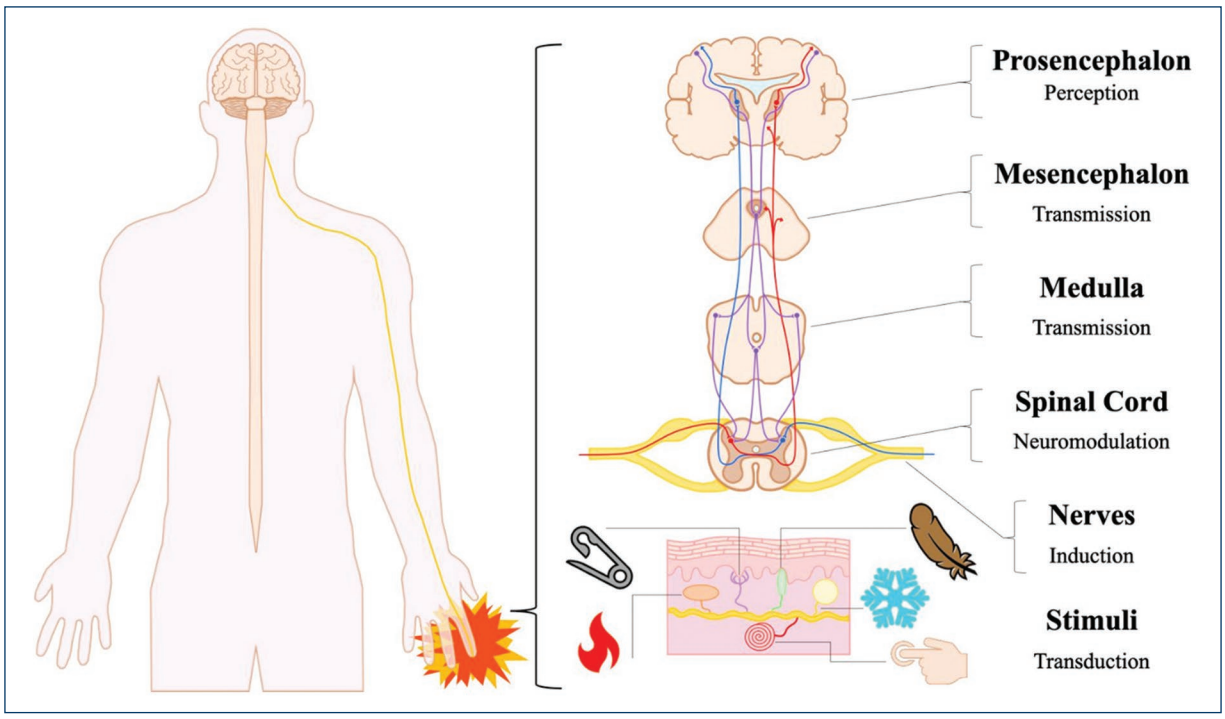


Figure 1. Anatomy and physiology of neuropathic pain.

and the C fibers, with a slower speed, for sustained pain. The neurotransmitters involved would be of a different nature depending on their origin. The main substances are tachykinins such as substance P (Pain), or prostaglandins, glutamate and aspartate, bradykinin, or ions such as chlorine[2,3]. Figure 2 shows these components.

Therapeutics

The understanding of anatomy together with physiology marks the way to achieve a multimodal treatment to be followed: rehabilitation is established in those patients in whom pain is tolerable, otherwise it increases with movements. Therapies can be performed (use of infrared rays, ultrasound, magnetic fields; TENS among others) on the relaxation of nearby muscles that improve compressive symptoms in a duct through which the nerves pass[4,5]. The second type is the use of different GABA-enhancing drugs as an inhibitory drug, or the use of glutamatergic antagonists, as they are excitatory. In this way, the main neuromodulators are antiepileptics (interacting with sodium, calcium, or chlorine channels) or antidepressants (promoting the increase of serotonin or norepinephrine in the synaptic terminals). New neuromodulatory drugs may have a dual action for both improving neuropathic pain and depression (breaking a pain-anxiety-depression cycle) ultimately improving pain[2]. Normally, the algology service can collaborate in an important way when performing nerve blocks, in which the nerve is infiltrated through the use of steroidal anti-inflammatory drugs alone or in combination with local anesthetics such as xylocaine or bupivacaine, either isolated or in combination with the possible modification of medications or doses[2,6]. An escalation can be made in cases where the pain is very intense using morphine or one of its derivatives such as buprenorphine or oxycodone following the WHO promotion scheme. Finally, the use of neurosurgery for pain is a last option, in which lesional or neuromodulatory procedures are found in the peripheral nerve, spinal cord, or at the brain level[3,6]. Among the interventions on the nerve are total or partial neurotomies, which are currently not recommended. Although neurolysis can be performed with good results for the plexus or some nerves, electrodes have also been placed on the peripheral nerve or cranial nerve, with satisfactory results[7,8]. Special consideration is the decompression of cranial nerves from vascular insult over the V of IX facial nerves[9], and the use of radiofrequency or radiosurgery is well effective in pain amelioration[10,11]. On the other hand, spinal cord injury has been beneficial with the use of cordotomies, medial myelotomies, or posterior rhizotomies, with their current use being

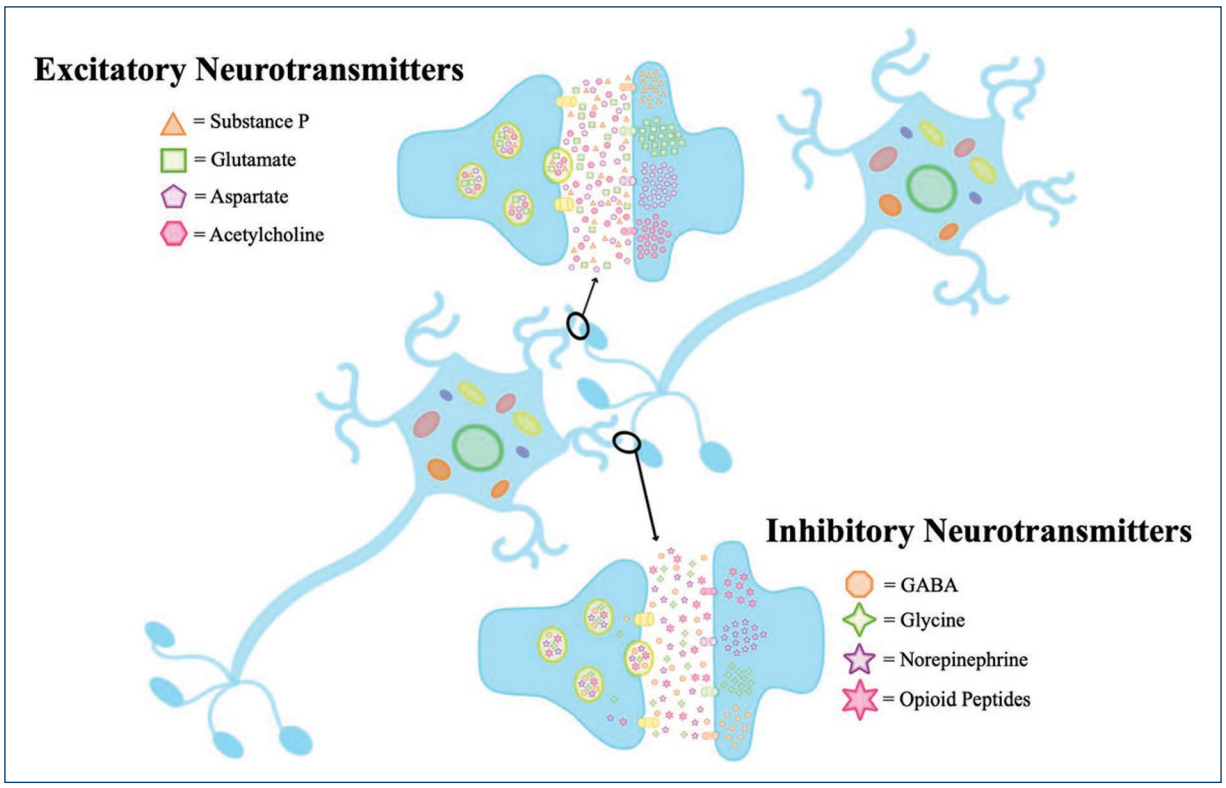


Figure 2. Neurotransmitters in production and abolition of pain.

Table 1. Lesional procedures for pain syndromes

Anatomical site	Procedure	Indication
Peripheral nerve	Neurotomy Neurolysis	Neurofibroma, neuroma, and compressive nerve pain
Cranial nerve	Baloon, glycerol, and RFR MVD Radiosurgery	V Neuralgia
	RFR and MVD Radiosurgery	IX Neuralgia
Spinal cord	DREZotomy	Deafferentation pain, brachial plexus injury, and spasticity
	Cordotomy	Cancer pain
	Medial myelotomy	Limb pain and spasticity
Brain	Thalamotomy	Deafferentation pain, cancer, and central pain. Contralateral limb pain
	Mesencephalic tracheotomy	Unilateral head pain, facial, and neck pain

RFR: radiofrequency rhizotomy; MVD: microvascular decompression.

very limited. The DREZotomy (Dorsal Root Entry Zone), which is a dorsolateral myelotomy, has been found to be more effective in patients with neuropathic pain[3]. As for neuromodulatory procedures, there are two: stimulation of the spinal cord percutaneously or by surgery, with good to very good results in close to 70% of cases. There is also the implantation of programmable infusion pumps where morphine, bupivacaine, and clonidine among other drugs are infused directly into the subarachnoid space, being effective in their use[6].

Table 2. Neuromodulation procedures for pain syndromes

Anatomical site	Procedure	Indication
Peripheral nerve	Nerve stimulation	Deafferentation pain and nerve tumor
Cranial nerve	Nerve stimulation	V, IX Neuralgia
Spinal cord	Posterior stimulation	Herpes Zoster, RCS, and spasticity
	Infusion pump	Cancer pain, RCS, and spasticity
Brain	Mesencephalic stimulation	Facial pain and post-ictus pain
	Hypothalamic nucleus	Aggressive cluster headache
	Thalamic stimulation	Contralateral limb pain and Dejerine–Roussy syndrome
	Motor cortex stimulation	Herpetic pain, phantom limb, and atypical facial pain

RCS: regional complex syndrome.

As for brain procedures, which are the last step when the others have failed, there is a radiofrequency injury to the thalamic nuclei such as the parafascicular or the centromedian nucleus. It has also been done on the cingulate with multiple lesions, or on the mesencephalic periaqueductal gray matter to abolish neuropathic pain. In addition, pituitary adenolysis is used in patients with mixed pain in terminal cancer conditions. With respect to neuromodulation, there is deep brain stimulation in the same sites mentioned for the injury[12], but also stimulation of the motor cortex has very good results[13,14]. Tables 1 and 2 summarize the above.

Conclusions

Understanding the concept of neuropathic pain, and its pathophysiology with the initial response of the receptors, with transmission, neuromodulation, and sensory perception is fundamental in medicine. It involves both fibers and neurotransmitters, and this applies to therapeutics that involve rehabilitation, medications, blocks, or in the latter case, lesional or neuromodulatory surgical interventions on the nerve, spinal cord, or brain.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript.

References

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised international association for the study of pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161: 1976-82.
2. González-Hermosillo DC, González-Hermosillo LM, Villaseñor-Almaraz M, Ballesteros-Herrera D, Moreno-Jimenez S, Corona-Cedillo R, et al. Current concepts of pain pathways: a brief review of anatomy, physiology, and medical imaging. Curr Med Imaging. 2024;(20):1-17. DOI:10.2174/1573405620666230519144112
3. Carrillo-Ruiz JD. La neuromodulación en el tratamiento del dolor. Dol Clin Ter. 2003;11:9-14.
4. Carrillo-Ruiz JD, Cortés-Contreras AP, Salazar AA, Cid-Rodríguez FX, González-Morales HF, García-Jerónimo AI, et al. Positive sensory symptoms, in surgically managed patients with carpal tunnel syndrome: a long term follow-up. Exp Ther Med. 2024;28:401.
5. González-Echeverría KE, Esqueda-Liquidano MA, Ariñez-Barahona E, Latorre-Dávila CA, Carrillo-Ruiz JD. Changes of neuropathic pain in two patients with thoracic outlet syndrome due to accessory cervical rib. Rev Mex Neuroc. 2018;19:39-48.
6. Deer TR, Prager J, Levy R, Rathmell J, Buchser E, Burton A, et al. Polyanalgesic consensus conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation. 2012;15(5):436-66. Erratum in: Neuromodulation. 2013; 16(4):38.
7. Armas-Salazar A, Téllez-León N, García-Jerónimo AI, Villegas-López FA Navarro-Olvera JL, Carrillo-Ruiz JD. Neuropathic pain relief after surgical neurolysis in patients with traumatic brachial plexus injuries: a preliminary report. Pain Res Manag. 2022;2022: 5660462.

8. García-Jerónimo AI, Armas-Salazar A, García-Muñoz L, Navarro-Olvera JL, Esqueda-Liquidano MA, Carrillo-Ruiz JD. Neuropathic pain and positive sensory symptoms in brachial plexus neuropathy: an exploratory study of outcomes after surgical decompression and proposal of a new sensory frequency of symptoms scale. J Integr Neurosci. 2023;22:25.
9. Carrillo-Ruiz JD, Covaleda-Rodriguez JC, Díaz-Martínez JA, Vallejo-Estrella A, Navarro-Olvera JL, Velasco-Campos F, et al. Minimally invasive retrosigmoidal parasterional burr-hole approach: technique and neuropathic pain amelioration after microvascular decompression of the trigeminal nerve. Biomedicines. 2023;11:2707.
10. Altamirano JM, Jimenez-Olvera M, Moreno-Jimenez S, Gutierrez-Aceves GA, Velasco-Campos F, Navarro-Olvera JL, et al. Comparison of microvascular decompression, percutaneous radiofrequency rhizotomy, and stereotactic radiosurgery in the treatment of trigeminal neuralgia: a long term quasi-experimental study. Pain Pract. 2024;24:514-24.
11. Gomes-da Silva De Rosenzweig P, Pastrana-Brandes S, Merikansky GS, Victoria-Garcia LO, Curtius-Caruso MS, Carrillo-Ruiz JD. Factors associated with outcomes following microvascular decompression for the treatment of primary trigeminal neuralgia in adults: a systematic review and meta-analysis. J Dent Anesth Pain Med. 2024;24:227-43.
12. Carrillo-Ruiz JD, Carrillo-Márquez JR, Beltrán JQ, Jiménez-Ponce F, García-Muñoz L, Navarro-Olvera JL, et al. Innovative perspectives in limbic surgery using deep brain stimulation. Front Neurosci. 2023;17:1167244.
13. Velasco F, Argüelles C, Carrillo-Ruiz JD, Castro G, Velasco AL, Jiménez F, et al. Efficacy of motor cortex stimulation in the treatment of neuropathic pain: a randomized double-blind trial. J Neurosurg. 2008;108:698-706.
14. Velasco F, Carrillo-Ruiz JD, Castro G, Argüelles C, Velasco M, Kassian A, et al. Motor cortex electrical stimulation applied to patients with complex regional pain syndrome. Pain. 2009;147:91-8.

Revista Médica del
Hospital General de México

PERMANYER

Check for updates

ORIGINAL ARTICLE

Liver disease in children with cystic fibrosis: observational study

Alejandra Sabillón, Flora Zárate-Mondragón, Rubén Peña-Vélez, Ana I. Quesada, and Jaime Ramírez*

Department of Gastroenterology and Nutrition, Instituto Nacional de Pediatría, Secretaría de Salud, Mexico City, Mexico

Abstract

Introduction: *Cystic fibrosis (CF) is a genetic disease of autosomal recessive inheritance, characterized by dysfunction of the exocrine secretion glands. The liver is an affected organ, which causes an increase in early morbidity and mortality.* **Objective:** *To evaluate liver disease in a group of children with CF.* **Material and methods:** *A total of 82 children with CF confirmed with genetic testing were included. Biochemical liver function tests and liver ultrasound were evaluated. The presence of fibrosis was estimated using the aspartato aminotransferasa to platelet ratio index (APRI) and correlation tests were performed.* **Results:** *59.8% (n = 49) of patients had elevated alanine aminotransferase. 30.5% (n = 25) showed an APRI suggestive of fibrosis. The correlation of APRI with alanino aminotransferase was 0.685 (p < 0.001) and with GGT 0.385 (p < 0.001). The prevalence of alterations in hepatic echogenicity was lower than biochemical alterations in transaminases.* **Conclusions:** *There is a high prevalence of liver disease at the diagnosis of CF and even a third of children could present with liver fibrosis. In this study, we found no difference in liver function tests according to liver ultrasound.*

Keywords: *Cystic fibrosis. Liver fibrosis. Transaminases.*

Introduction

Cystic fibrosis (CF) is a disease of genetic origin, with autosomal recessive inheritance that is diagnosed mainly in children. It is caused by pathogenic variants in the CF transmembrane conductance regulator (CFTR) gene. The main system affected is the respiratory tract and pancreas. There is also the involvement of the sweat glands, the intestine, the nasal mucosa, the salivary glands, and the reproductive system[1].

The liver is a frequently compromised organ[2], liver damage develops within the first 20 years of life and is usually stable, with a slowly progressive evolution[3]; however, some children may develop liver cirrhosis in early childhood or adolescence[4]. Determining the coexistence of liver disease is important, as it has a relevant implication in the short- and long-term prognosis of children with CF[5].

The objective of this study was to determine the prevalence and characteristics of liver disease by evaluating liver function tests in a group of children with CF at the time of diagnostic confirmation.

Methods

A retrospective analytical study included 82 children with a confirmed genetic diagnosis of CF, treated in the Pediatric Gastroenterology and Nutrition service at Instituto Nacional de Pedriatría (Mexico City, Mexico). Baseline liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltranspeptidase, alkaline phosphatase, albumin, lipids, bilirubin's,

***Correspondence:**
Alejandra Sabillón
E-mail: alesabillon@yahoo.com

Date of reception: 04-03-2024
Date of acceptance: 04-07-2024
DOI: 10.24875/HGMX.24000018

Available online: 01-04-2025
Rev Med Hosp Gen Mex. 2025;88(2):62-65
www.hospitalgeneral.mx

and INR) were collected. The cutoff point of the SAFETY study[6] was used for the detection of chronic liver disease in children, considering the elevation of alanino aminotransferase (ALT) > 22.1 U/L in girls and 25.8 U/L in boys. The aspartato aminotransferasa (AST) to platelet ratio index (APRI) was calculated using the formula proposed by Wai et al.[7]. (APRI = [patient AST level/AST upper limit normal] × 100/platelet count 10^9/L), which was interpreted: < 0.5 = no significant fibrosis, 0.5-1.5 = probable fibrosis, and > 1. 5 = significant fibrosis.

Statistical analysis

The distribution of normality was evaluated with the Kolmogorov–Smirnov test. Subsequently, descriptive statistics were performed. The means were compared with the Mann–Whitney U test and correlations were made with the Sperson test. Statistical significance was established with an alpha error < 0.05. The analysis was performed in the SPSS version 22 software.

Bioethics

The study complies with current bioethical regulations on international recommendations for research in humans and adheres to the research guidelines of the Instituto Nacional de Pedriatría.

Results

A total of 82 children diagnosed with CF were included. The median age at diagnosis was 10 months (interquartile range = 30). 59.8% (n = 49) of the patients had elevated ALT in the first biochemical evaluation after diagnosis, the means of the other liver function tests are presented in table 1.

Of 69.5% (n = 57) had APRI between 0-0.5 (without fibrosis), 24.4% (n = 20) had APRI between 0.5-1.5, and 6.1% (n = 5) had APRI > 1.5. The correlation of APRI with ALT was 0.685 (p < 0.001), with AST 0.804 (p < 0.001), and with GGT 0.385 (p < 0.001), no correlation was found with other liver function tests (Table 2). When comparing liver function tests according to sex, we did not find significant differences, nor a greater association of ALT elevation in boys or girls (p = 0.159).

The most frequent genetic mutations were F508del (n = 14) and G542X (n = 9), no difference was found between the two groups in the comparison of liver function tests.

The children included in this study underwent liver ultrasound and 39% (n = 32) had alterations consistent with changes in liver echogenicity; however, when comparing the liver function tests of the children with and without liver ultrasound alterations, no differences were found (Table 3).

Table 1. Liver function tests and biochemical parameters in children with cystic fibrosis

Parameters	Median and interquartile range
ALT	32 (41)
AST	49 (41)
ALP	194 (166)
GGT	33 (54)
Platelets	350,000 (187,000)
Albumin	3.30 (1.3)
INR	1.03 (0.20)
BT	0.57 (0.40)
BD	0.17 (0.22)
Vitamin D	18 (11)
CT	111 (48)
Triglycerides	98 (55)
APRI	0.34 (0.38)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyltranspeptidase; INR: *International normalized ratio;* BT: total bilirubin; BD: direct bilirubin; CT: total cholesterol; APRI: AST to platelet ratio index.

Discussion

In this study, we found that more than half of the children with the confirmatory diagnosis of CF had elevated transaminases. It has been described that CF-associated liver disease occurs due to alteration in the cholangiocyte transport protein, which results in chronic cholangiopathy secondary to a reduction in ductal bile flow, bile chloride, and bicarbonate secretion due to CFTR dysfunction[8]. However, the mechanism of liver injury is considered to be multifactorial, including the CFTR genotype, non-CFTR genetic variability, abnormal intracellular interactions, abnormal cholangiocyte function, impaired bile secretion, and pathological stimulation of the innate immune response with an abnormal response to endotoxins[2,9].

The prevalence of liver disease in children with CF is varied and has been reported to occur in 5% to 68%, depending on the criteria used for its diagnosis[10,11]. Risk factors include male sex, the presence of severe

Table 2. APRI correlation tests with biochemical parameters and liver function tests

	ALT	AST	ALP	GGT	Albumin	Vit D
Correlation	0.685	0.804	0.47	0.385	–0.068	–0.248
p	< 0.001	< 0.001	0.675	< 0.001	0.547	0.043

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyltranspeptidase.

Table 3. Comparison of liver function tests according to liver ultrasound abnormalities in children with cystic fibrosis

	Altered USG	Normal USG	p
ALT	56.16 ± 69	38.73 ± 32	0.393
AST	121.16 ± 195	39.86 ± 12	0.119
ALP	187.91 ± 87	177.40 ± 87	0.759
GGT	82.58 ± 41	41 ± 37	0.219
Platelets	347,000 ± 94,000	402,000 ± 138,000	0.250
Albumin	3.3 ± 0.9	3.2 ± 0.7	0.692
BT	1.3 ± 1	0.5 ± 0.29	0.72
APRI	1.1 ± 2.2	0.29 ± 0.17	0.164

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyltranspeptidase; INR: *International normalized ratio*; BT: total bilirubin; APRI: AST to platelet ratio index.

mutations, the presence of the *SERPINE 1Z* allele, a history of meconium ileus, exocrine pancreatic insufficiency, and CF-associated diabetes[12]. In our study, we found no difference in the alteration of liver function tests according to sex. The most frequently reported mutations in patients were F508del and G542X, with no major difference in liver involvement observed according to the type of mutation.

In our study, we used the *APRI* to estimate the presence of liver fibrosis in children with CF. At present, there are different validated non-invasive methods to evaluate liver disease in the adult population[13] and some have been used in the pediatric age with different results. APRI has shown good diagnostic performance in establishing the diagnosis of fibrosis in children with NAFLD (AUROC 0.619, 95% CI 0.556-0.679, p < 0.001)[14]; however, it seems to be superior in establishing liver involvement in children with CF. A study that evaluated the usefulness of non-invasive methods for diagnosing liver fibrosis in children with CF determined that the APRI is superior to the AST/ALT ratio, FIB-4 score, GGT, GGT/platelet ratio, and platelet count, showing an AUROC of 0.90; 95%CI = 0.830-0.970; p = 0.0380. The same study indicated that the elevation of the APRI cutoff point of ≥ 0.425 has an odds ratio of 23.8 (95%CI = 5.2-109.7; p < 0.001) for CF-associated liver disease[15]. Liver biopsy was not performed in our patients, which is a deficiency to be considered in this study; however, other studies in children with CF have indicated that APRI is a good surrogate marker to establish the presence of liver fibrosis[16,17].

In the annual follow-up of children with CF, it is recommended that transaminases be evaluated and if alterations are found, hepatic ultrasound is initiated[18]. Partial or total hepatic hyperechogenicity is suggestive of steatosis and is the most common ultrasound finding in children with CF[19]. The patients included in this study were also evaluated by liver ultrasound, finding alteration of hepatic echogenicity in 39%; however, when comparing transaminases and other liver function tests, no difference was found, even though the percentage was lower in children with elevated transaminases. This is in contrast to other studies; abnormal echogenicity has been reported to precede biochemical or clinical evidence of liver disease. One study shows that two-thirds of children with abnormal hepatic echotexture and 50% with portal hypertension had no biochemical or clinical evidence of CF-associated liver disease at the time ultrasound changes were first observed[20]. It should be considered that ultrasound is an operator-dependent study and that there is intra- and interobserver variability in ultrasound images, and children with normal liver ultrasound may have advanced fibrosis, so a normal ultrasound does not exclude significant liver fibrosis[3]. A weakness of the study is that only biochemical tests of liver function and ultrasound were available, and ideally, elastography or other surrogate markers should be included for the evaluation of liver fibrosis and correlation tests should be performed to validate our findings.

Conclusion

In this study, we found that more than half of the children with CF at diagnosis may have elevated transaminases

and according to the APRI estimate, 30.5% may have liver fibrosis, also observing a good correlation of APRI with other liver function tests. In this study, we observed that liver ultrasound may be normal, even when there is biochemical evidence of liver disease.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. López-Valdez JA, Aguilar-Alonso LA, Gándara-Quezada V, Ruiz-Rico GE, Ávila-Soledad JM, Reyes AA, et al. Cystic fibrosis: current concepts. Bol Med Hosp Infant Mex. 2021;78:584-96.
2. Valamparampil JJ, Gupte GL. Cystic fibrosis associated liver disease in children. World J Hepatol. 2021;13:1727-42.
3. Lindblad A, Glaumann H, Strandvik B. Natural history of liver disease in cystic fibrosis. Hepatology. 1999;30:1151-8.
4. Leung DH, Narkewicz MR. Cystic fibrosis-related cirrhosis. J Cyst Fibros. 2017;16 Suppl 2:S50-61.
5. Ye W, Narkewicz MR, Leung DH, Karnsakul W, Murray KF, Alonso EM, et al. Variceal hemorrhage and adverse liver outcomes in patients with cystic fibrosis cirrhosis. J Pediatr Gastroenterol Nutr. 2018;66:122-7.
6. Schwimmer JB, Dunn W, Norman GJ, Pardee PE, Middleton MS, Kerkar N, et al. SAFETY study: alanine aminotransferase cutoff values are set too high for reliable detection of pediatric chronic liver disease. Gastroenterology. 2010;138:1357-64, 1364.e1-2.
7. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003;38:518-26.
8. Staufer K, Halilbasic E, Trauner M, Kazemi-Shirazi L. Cystic fibrosis related liver disease-another black box in hepatology. Int J Mol Sci. 2014;15:13529-49.
9. Fiorotto R, Strazzabosco M. Pathophysiology of cystic fibrosis liver disease: a channelopathy leading to alterations in innate immunity and in microbiota. Cell Mol Gastroenterol Hepatol. 2019;8:197-207.
10. Dos Santos AL, De Melo-Santos H, Nogueira MB, Távora HT, Da Cunha MD, De Melo-Seixas RB, et al. Cystic fibrosis: clinical phenotypes in children and adolescents. Pediatr Gastroenterol Hepatol Nutr. 2018;21:306-14.
11. Lamireau T, Monnereau S, Martin S, Marcotte JE, Winnock M, Alvarez F. Epidemiology of liver disease in cystic fibrosis: a longitudinal study. J Hepatol. 2004;41:920-5.
12. Staufer K. Current treatment options for cystic fibrosis-related liver disease. Int J Mol Sci. 2020;21:8586.
13. Mózes FE, Lee JA, Selvaraj EA, Jayaswal AN, Trauner M, Boursier J, et al. Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient data meta-analysis. Gut. 2022;71:1006-19.
14. Mosca A, Della-Volpe L, Alisi A, Veraldi S, Francalanci P, Maggiore G. Non-invasive diagnostic test for advanced fibrosis in adolescents with non-alcoholic fatty liver disease. Front Pediatr. 2022;10:885576.
15. Karnsakul W, Wasuwanich P, Ingviya T, Vasilescu A, Carson KA, Mogayzel PJ, et al. A longitudinal assessment of non-invasive biomarkers to diagnose and predict cystic fibrosis-associated liver disease. J Cyst Fibros. 2020;19:546-52.
16. Leung DH, Khan M, Minard CG, Guffey D, Ramm LE, Clouston AD, et al. Aspartate aminotransferase to platelet ratio and fibrosis-4 as biomarkers in biopsy-validated pediatric cystic fibrosis liver disease. Hepatology. 2015;62:1576-83.
17. Woolfson JP, Schreiber RA, Raveendran S, Chilvers M, Barker C, Guttman OR. Role of transient elastography and APRI in the assessment of pediatric cystic fibrosis liver disease. Can Liver J. 2021;4:23-32.
18. Debray D, Kelly D, Houwen R, Strandvik B, Colombo C. Best practice guidance for the diagnosis and management of cystic fibrosis-associated liver disease. J Cyst Fibros. 2011;10:S29-36.
19. Akata D, Akhan O. Liver manifestations of cystic fibrosis. Eur J Radiol. 2007;61:11-7.
20. Lenaerts C, Lapierre C, Patriquin H, Bureau N, Lepage G, Harel F, et al. Surveillance for cystic fibrosis-associated hepatobiliary disease: early ultrasound changes and predisposing factors. J Pediatr. 2003;143:343-50.

Revista Médica del
Hospital General de México

PERMANYER

Check for updates

ORIGINAL ARTICLE

Measurement of neuropathic pain in constrictive sciatic nerve models in rats

*José R. Carrillo-Márquez[1,2], Ma. Fernanda Carrillo-Márquez[1,2], José L. Navarro-Olvera[3], Jesús Q. Beltrán[3], Alfonso Ceniceros-Obregón[1,2], Luis M. Rodríguez-Serrano[5], and José D. Carrillo-Ruiz[3,4,5]**

[1]Faculty of Health Sciences; [2]Alpha Health Sciences Leadership Program. Universidad Anahuac; [3]Stereotactic, Functional and Radiosurgery Unit of Neurosurgery Service; [4]Research Direction. Hospital General de México Dr. Eduardo Liceaga, Secretaría de Salud; [5]Faculty of Psychology, Neuroscience Coordination, Universidad Anahuac. Mexico City, Mexico

Abstract

Introduction: *Neuropathic pain occurs due to algogenic stimuli in the nervous system. The sciatic nerve constriction is one of the most popular models used to understand neuropathic pain in rats.* **Objective:** *Describe different techniques to measure neuropathic pain in rats.* **Materials and methods:** *The platforms of PubMed, Scopus, and Google Scholar were used to identify the way of measuring neuropathic pain in rats using the sciatic nerve constriction technique (Bennett technique) between 1988 and 2024. Boolean operators and medical subject headings terms were used to search papers including "neuropathic pain", "sciatic constriction", "rats", "measurement" and "evaluation." The inclusion criteria were: (1) studies in rats, (2) use of sciatic nerve constriction technique as production of neuropathic pain, (3) measurement of neuropathic pain in rats. Exclusion criteria were: (1) review articles and (2) articles in a language other than English, French, or Spanish, (3) incomplete or non-specific measurement articles.* **Results:** *Of 17,900 articles, a total of (n = 132) were selected in which neuropathic pain was measured in rats. The following percentages show the frequency of the forms of measurement used in the literature: (1) von Frey Filament Test: 99 (75%) of the articles, (2) hot stimuli: 80 (60.60%) of the items, (3) Cold score: 40 (30.30%) of the articles, (4) pin Pricking: 5 (3.78%) of the items, and (5) other forms of measurement: 41 (31.06%).* **Conclusions:** *There are multiple tests to measure pain and can be used in therapeutic studies to improve pain. The Von Frey Filament test is the most used technique to understand sensitive stimuli in constrictive sciatic neuropathic pain models in rats.*

Keywords: *Neuropathic pain. Bennett technique. Sciatic nerve. Measurement. Evaluation, rats.*

Introduction

Pain is described as an unpleasant sensation in the organism[1]. Neuropathic pain can be expressed as a stimulation of the algogenic receptors caused by a lesion to the peripheric or central nervous system[2,3]. There has been an increment in invertebrate and small mammal (*i.e.,* mice, rats, bunnies) models aiming to understand molecular mechanisms of action, as neurons and fibers are involved in transmitting pain[4,5]. Furthermore, different therapeutic possibilities have been researched, including medications, biological substances, and other neuromodulators that might shift treatment options[6].

The constriction of the sciatic nerve is one of the most popular models used to understand neuropathic pain. This article will exhaustively describe the existing tests and experiments in the scientific literature. The objective of this review is to display the different forms of measuring pain and the specific techniques that are used in sciatic nerve constriction in rat models[4].

***Correspondence:**
José D. Carrillo-Ruiz
E-mail: josecarrilloruiz@yahoo.com

Date of reception: 16-01-2024
Date of acceptance: 21-08-2024
DOI: 10.24875/HGMX.24000007

Available online: 21-11-2024
Rev Med Hosp Gen Mex. 2025;88(2):66-73
www.hospitalgeneral.mx

Materials and methods

This review used the National Library of Medicine standard research protocol to obtain its bibliography. We used public and free meta-search engines such as PubMed, Scopus, and Google Scholar. To identify the articles measuring neuropathic pain with sciatic nerve constriction technique in rats (Bennett technique), we selected a time lapse between 1988 and 2024. To correctly filter the scientific literature, Boolean Operators were used with the upcoming Medical Subject Headings (MeSH): neuropathic pain, sciatic constriction, rats, measurement, and evaluation.

The inclusion criteria were: (1) studies in rats; (2) use of sciatic nerve constriction technique (Bennett technique) to produce neuropathic pain; and (3) measurement of neuropathic pain in rats. The exclusion criteria were: (1) review articles, (2) articles that were not written in English, French, or Spanish; and (3) incomplete or non-specific measurement articles. A total of 132 articles were selected (Fig. 1).

Bennett technique or sciatic nerve constriction model

The Bennett technique was proposed in 1988 as the first rat model that recreated mononeuropathy in rats[7]. The steps to make this procedure are the following. First, the researcher must apply intraperitoneal anesthesia to the rat trying to induce sleep and nullify pain in the upcoming surgery, insulin needles are recommended for applying chloral hydrate or propofol. After the animal is set asleep, the lower right extremity that will be operated must be shaved with a hair clipper, and antisepsis should be done using chlorhexidine or povidone-iodine in the gluteal region and the leg of the rat. It is important to mention that the surgeon should use the proper equipment (*i.e.,* surgical gown, adequate surgical gloves, facemask, and aseptic surgical equipment) and antiseptic technique to reduce the probability of post-surgical infections, as shown in figure. 2.

Subsequently, the skin should be cut with a #15 scalpel, and dissection should be done with Mayo or Iris scissors, it may also be done with curved Kelly forceps. When the sciatic nerve has been located, a gentle dissection must be done with the curved Kelly forceps to preserve the nerve. This white structure must be exposed to pass under three 4-0 silk threads. These strings will be used to tie the nerve firmly 3 times. After that, the surgeon must do a layered closure using a 4-0 silk suture, starting with the muscle, and finishing with the skin. The recommended technique is the use of a simple interrupted suture. Finally, a single dose of prophylactic broad-spectrum antibiotic is used to lower the risk of future infections and complications[8].

Results

Different methods to measure pain

After inspecting the scientific literature, we found 132 articles that measure neuropathic pain in rats using sciatic nerve constriction. These articles can be divided into the following categories by using the methods in which the authors measured pain: (1) Von Frey test, (2) pin pricking test (3) cold score, (4) hot-plate test, and (5) miscellaneous. In the following paragraphs, the article will describe each method as well as the specifications of each measurement. We will display a figure to clarify how the tests are done.

It should be highlighted that out of all the papers that were selected (n = 132), the Von Frey filament test was used in 99 (75%) of the articles, Hot stimuli in 80 (60.60%) of the items, cold score in 40 (30.30%) of the articles, pin pricking in 5 (3.78%) of the items and Other forms of measurement in 41 (31.06%). In the following subdivisions, each technique will be described in this section.

Von Frey test

It can be said that the Von Frey filament test is the gold standard for measuring pain that produces allodynia from mechanical stimuli in rats. This measuring method can be applied either manually with different hair thicknesses, or with an electronic filament that applies increasing force until the extremity is withdrawn[9]. The manual filaments are a standardized set of 20 units that vary in the force applied to the rat extremity. The range of hairs goes from 0.008 to 300 g of force applied to its tip, which has a corresponding thickness between 1.65 and 6.65 mm as shown in table 1.

Although the electronic Von Frey test can be used, not every laboratory has this equipment for measuring pain. Moreover, pain can still be quantified accurately manually as well as electronically. The latter has a clear advantage, it reduces measurement times because the force is applied by the device and no instrument change is required. The hardware and software used for measuring neuropathic pain are Dynamic Plantar Esthesiometer and Mouse Met/Rat Met[10].

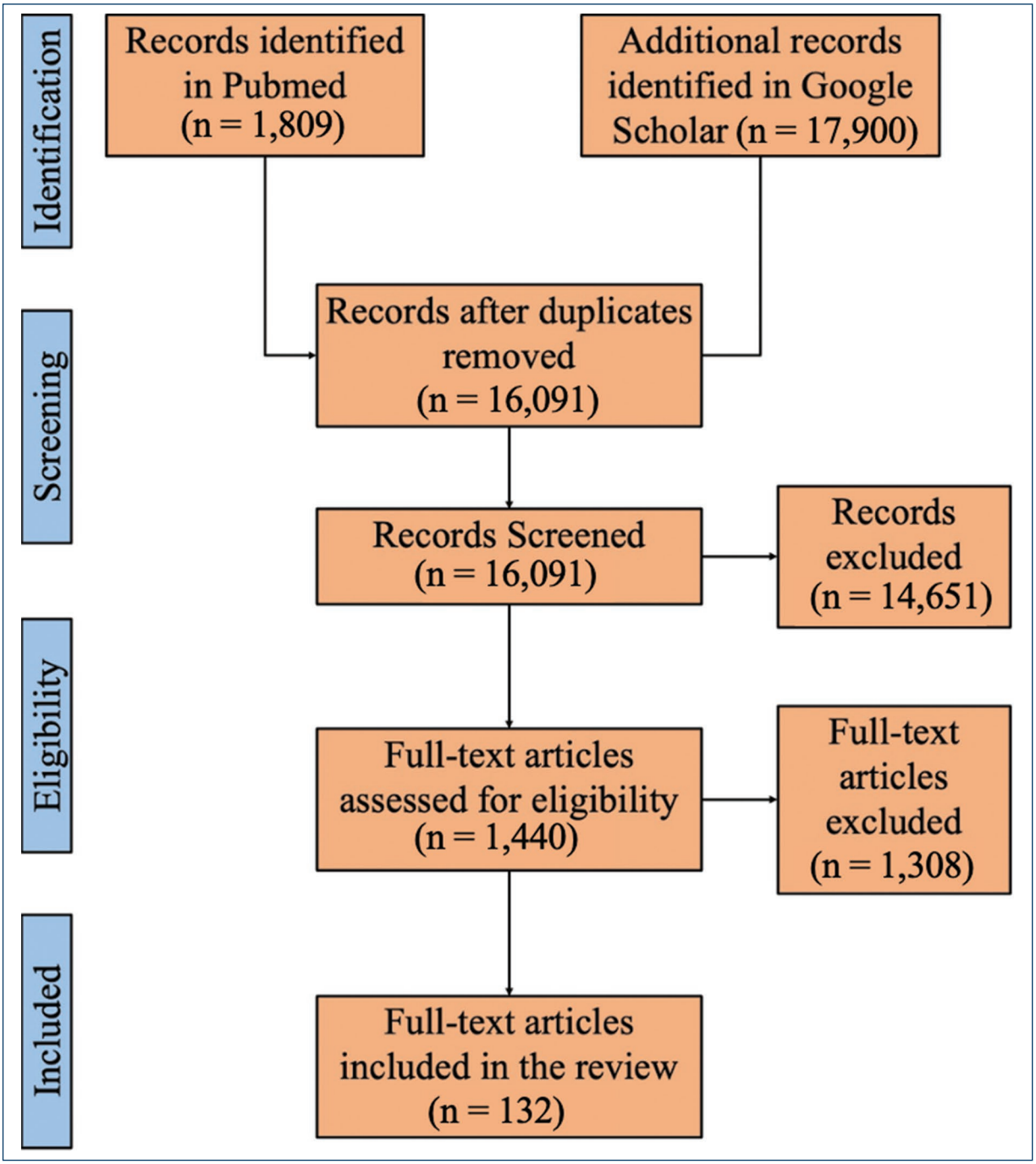


Figure 1. PRISMA flow diagram for paper selection. In this figure, the criteria used for selecting the scientific papers used in this review can be seen. It is important to state that the search started using the operators "(neuropathic pain) AND (sciatic constriction)" and after different exclusions the final search with Boolean operators was "(neuropathic pain) AND (sciatic constriction) AND (rats) AND (measurement) AND (evaluation)". This prompt reduced the number of articles from 17,900 to 132 eligible for making the review.

For using Von Frey hairs, it is essential to lay the animal under a meshed surface and use a transparent cage to determine the response to stimuli, as shown in figure. 3. A positive response is a clear withdrawal of the extremity or continuous repeated small movements because sometimes the extremities might have paresis. The most used methods for measuring pain are: "percentage response frequency," "ascending test" and

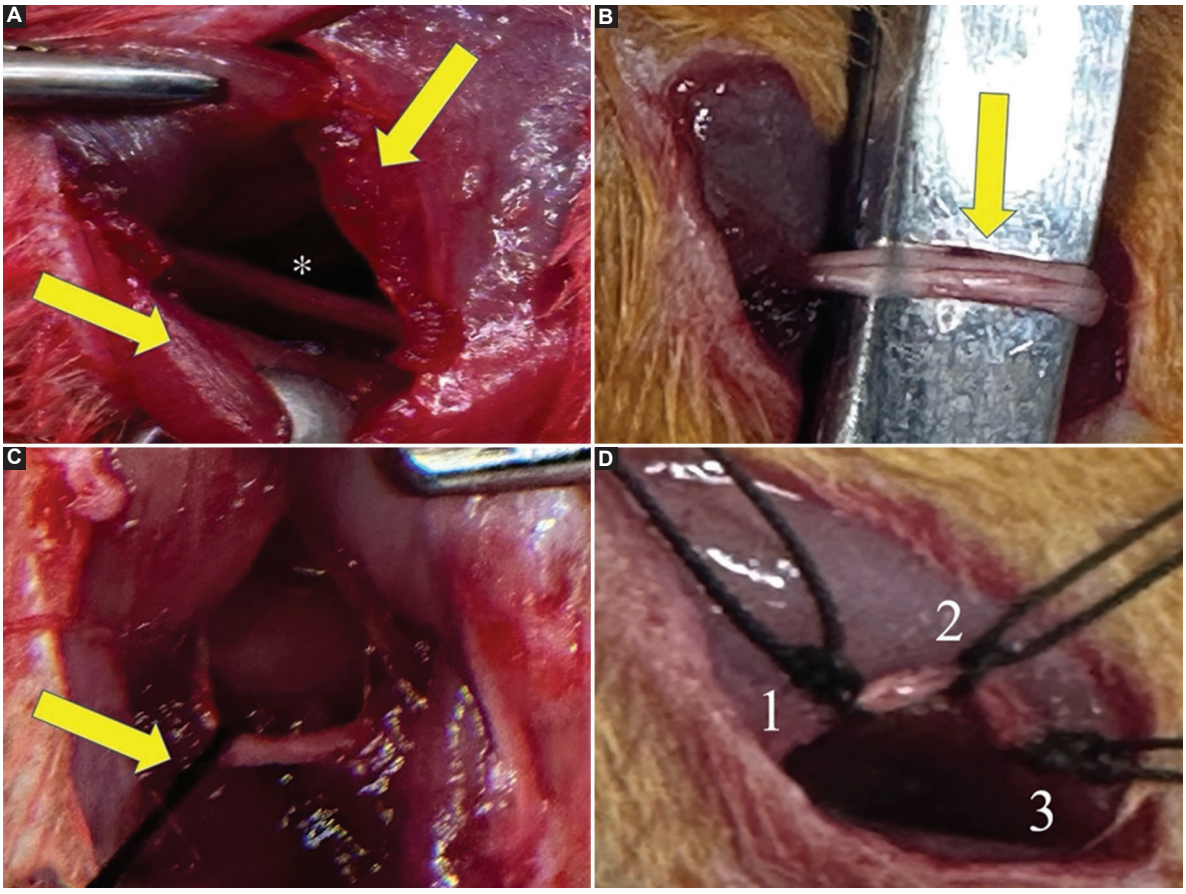


Figure 2. Bennett technique steps. In the upper images are shown the series of steps that are required for the Bennett technique for compressing the sciatic nerve. After previously completing the first steps mentioned before. **A:** shows the separation of the *gluteus maximus* and *biceps femoris* muscles; *: sciatic nerve. **B:** the sciatic nerve is located and exposed to realize the dissection. **C:** 4-0 silk thread that will be used for three knots. **D:** the image describes how the three knots should look like, and the correct spacing between them.

"up-down method." The "percentage response frequency" is the easiest way of measuring neuropathic pain because the hairs are used in ascending order, the same number of times proposed by the researchers (*e.g.,* 3 times, 6 times, 10 times) until the paw withdrawal is frankly positive, as Kim and Chung described[11]. A variation of the last method is the "ascending test" which consists of using hairs from thinnest to thickest until a positive response is seen 2 times in ten applications as Scholz et al. first proposed[12].

Finally, the "up-down method" was introduced in rats in 1944 by Chaplan SR, for measuring neuropathic pain in the lower extremities in rats. This method proposes using a 50% withdrawal threshold calculated by positive or negative responses. The test starts after selecting a filament if there is a positive response the immediate lower hair should be used, and if there is a negative one the upper filament should be used. A minimum of four tests should be done after the change of direction[13]. The Up-Down Reader software can help researchers obtain the correct filament size more efficiently and create more accurate statistics with this method[14].

Pin pricking test

This technique was initially described by Kingery and Vallin in 1989 for sciatic nerve section in a hyperalgesia model in rats. The pin pricking test is one of the simplest ways of measuring pain, and it consists of applying pressure to the paw of the rat in the plantar zone with a pin to determine if the animal moves upward the limb[15]. It should be pointed out that the person in charge of holding the animal must use bait gloves to reduce injuries while realizing this technique because rats tend

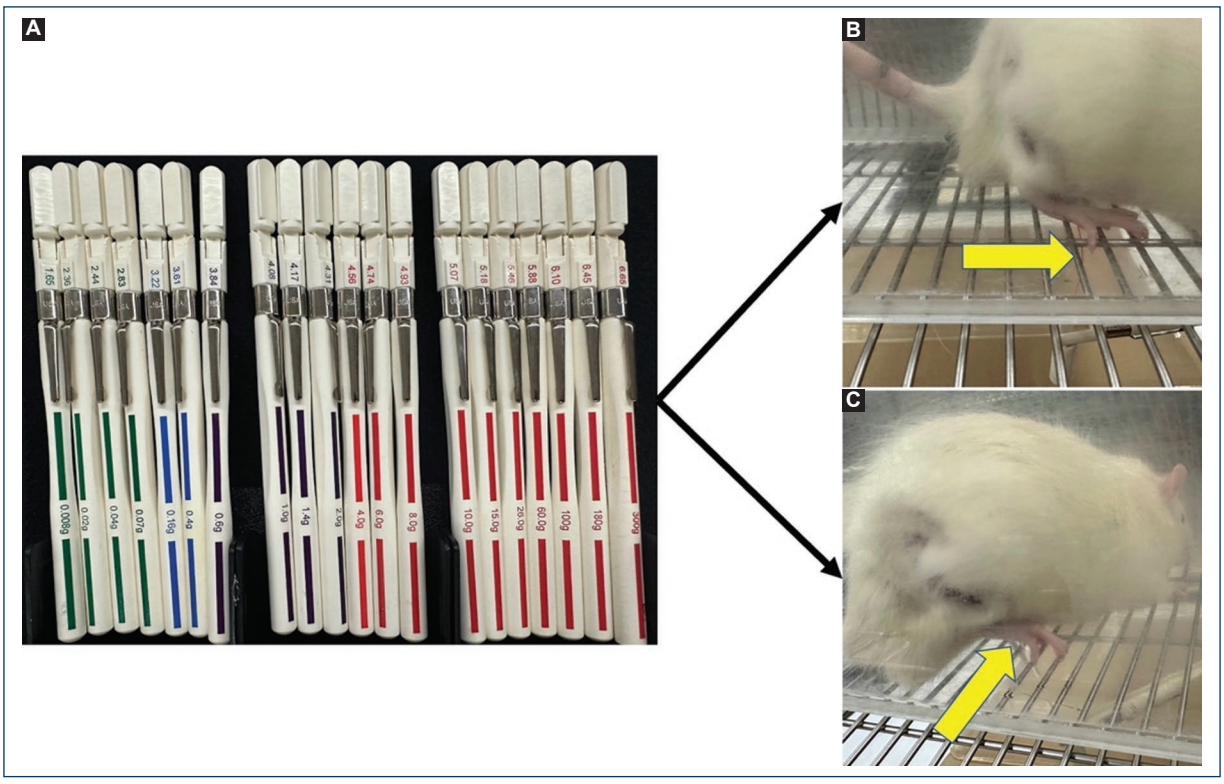


Figure 3. Von Frey test being held on a rat. In the upper image, it can be seen how a Von Frey test should be applied. **A:** shows the 20 tools for measuring the Von Frey test, which vary from 0.008 to 300 g. **B:** indicates no withdrawal of the extremity, thus it is a negative response. **C:** it is seen as a withdrawal of the rat's extremity, which indicates there is a positive response to the Von Fray test.

to react aggressively. The examiner should apply a moderate amount of pressure to lower the chances of penetrating the paw, and it should be said that the principal complication of this test is harming the animal[16], as shown in figure 4.

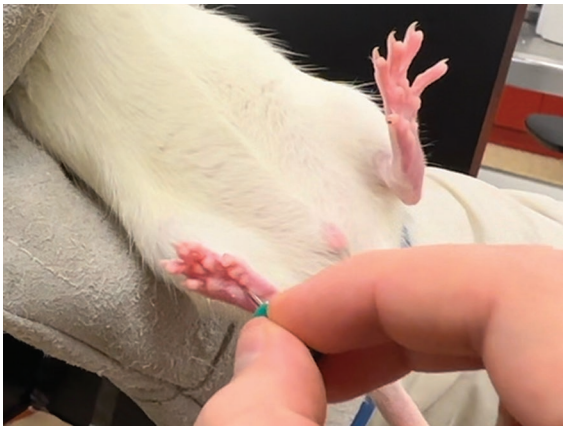


Figure 4. Pin pricking test on a rat's right feet. The pin pricking test is being done in the plantar area of the paw; it is perceived that the rat is moving upward the limb. This is the expected reflex on a normal rat.

Cold score

The cold score test was stated by Hao et al. in 1999 as a method to quantify neuropathic pain in rats in a sciatic nerve constriction model. The tests consist of applying a cold spray directly to the affected limb as shown in figure 5. The response to this test is measured in a scale created by the author that helps to understand allodynia induced by a cold stimulus as shown in table 2[17,18].

Hot-plate test

In 1944, Woolfe and MacDonald used for the 1st time the hot-plate test in mice for measuring discomfort during exposure to a metal surface. Although the methodology of this article was first used for pharmacological efficiency, nowadays the implementation of this technique has been replicated in various models for measuring pain as shown in table 3. This

Table 1. Von Frey filaments equivalences. Equivalence between filament label and force in grams applied

Filament label	Force (g)
1.65	0.008
2.36	0.02
2.44	0.04
2.83	0.07
3.22	0.16
3.61	0.4
3.84	0.6
4.08	1.0
4.17	1.4
4.31	2.0
4.56	4.0
4.74	6.0
4.93	8.0
5.07	10.0
5.18	15.0
5.46	26.0
5.88	60.0
6.10	100
6.45	180
6.65	300

Table 2. Cold score chart. Items establish the classification of each level of response to a cold stimulus

Cold score (Hao et al., 1999)[18]	
0	No response
1	Startle response without paw withdrawal
2	Brief withdrawal of the paw
3	Prolonged withdrawal of the paw
4	Repeated prolonged withdrawal and other reactions

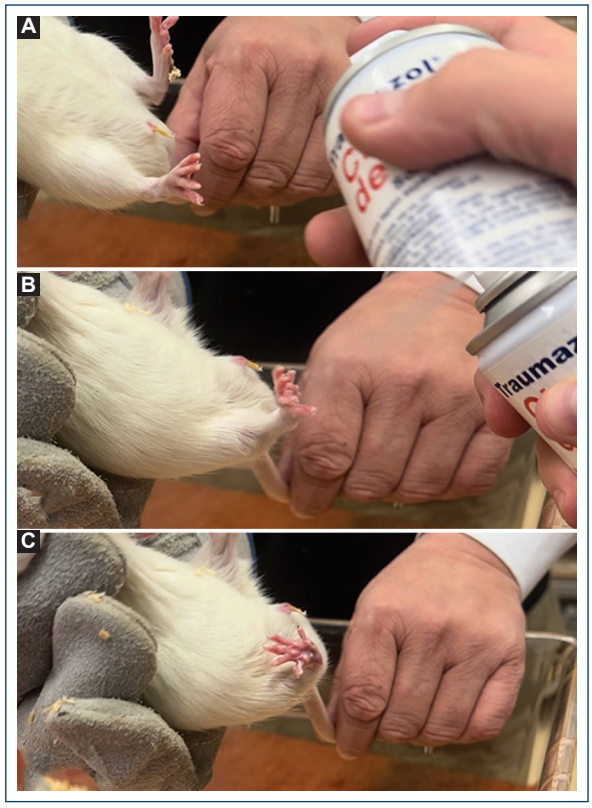


Figure 5. Methodology of cold score. The image shows the three steps to be followed when realizing the cold score methodology. **A:** prepare the rat for the test, placing the bottle spray in front of the rat's affected paw. **B:** spray is applied to the rat's feet. **C:** the leg is moved in an upward direction, confirming a positive test.

Table 3. Techniques found in the scientific literature for assessing allodynia and hyperalgesia from 1988 to 2024

No.	Technique	No. articles	Percentage
1	Von Frey	99	75
2	Hot stimuli	80	60.60
3	Others*	41	31.06
4	Cold score	40	30.30
5	Pin pricking	5	3.78
Total		132	100

This table represents the frequency of each diagnostic method for measuring pain from the 132 articles selected from the literature that realized the Bennett technique.
*In this section of the table the following methods are included: Dynamic weight bearing test (n = 1), duration of licking after injecting formalin (n = 8), open field test (n = 1), Randall-Selitto paw pressure test (n = 18), rotarod test (n = 7), spontaneous pain specific method (n = 3), cold plate test (n = 1), spontaneous pain (n = 2), weight-Erbearing test (n = 1), cotton bud test (n = 1), resting paw posture (n = 2), acetic acid (n = 1), tail-flick test (n = 1), vocalization threshold (n = 1), conditioned place preference (n = 1), free walking pattern (n = 1), neutral plate test (n = 1), sciatic function index (n = 1), Choi test (n = 1).

test is made by laying the paw of the animal on a surface with a temperature of 55°C, equivalent to 131°F, for an approximate time of half a minute, unless the animal starts to feel intense pain. The major complication of this technique is burning the rat's extremity[19].

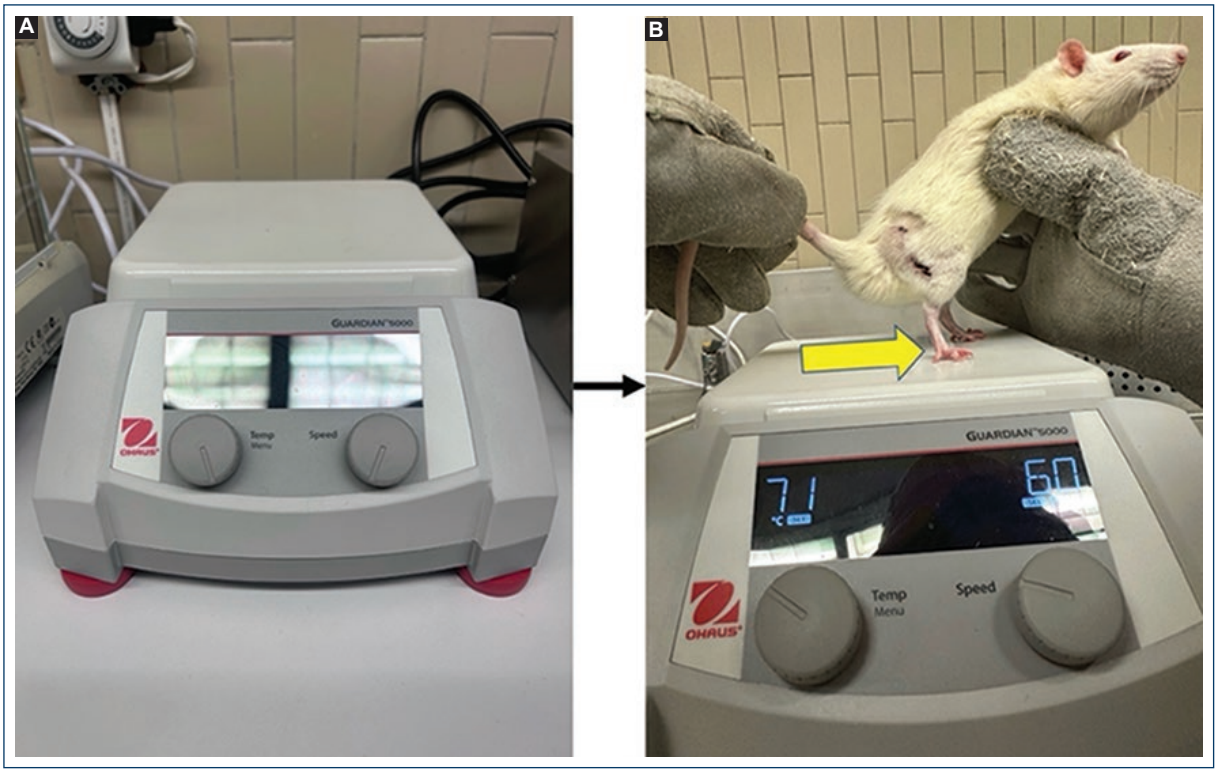


Figure 6. Hot-plate test image. As demonstrated in the image above, this test requires a machine that conducts heat into the plate. **A:** a hot plate device is shown without any form of heat being passed to the surface. **B:** an active device is being used to assess a pain test in the lower extremities of the rat.

Some of the latest articles published in 2021, also use a variation of the hot plate with focused infrared radiation to the paw[20,21], adapting the tail-flick test proposed in 1941 by D'Amour and Smith to the affected limb[22]. This variation of the hot plate is made with converging radiant heat. The paw thermal withdrawal time was first proposed by Hargreaves et al. back in 1988[23]. The hot-plate test is the gold standard to measure hyperalgesia with warm stimuli, as shown in figure. 6.

Miscellaneous

Some of the other methods found in the scientific literature can be seen in table 3. It is important to mention that these tests have been used to study neuropathic pain as alternative proposals or newly found methods. Other 19 different methods have been used, according to the search. It is vital to emphasize that every research group tries to measure pain with the material available in the laboratory. Furthermore, some of these scales might evaluate more efficiently their specific models, as shown in table 3.

Discussion

Bennet´s model is a successful and consistent one to produce, undoubtedly, neuropathic pain in rodents. This solid article was cited more than 7,000 times in the scientific literature and demonstrates the consolidation of this technique to produce pain with its diverse modalities including the responses to mechanical and thermic stimuli[7,8]. In our article, we well illustrated how the technique was performed and demonstrated the different measurements with several figures that help to exemplify how each test should be done with the rats.

Moreover, the systematic review showed that the most frequent evaluation was the use of the Von Frey filaments with 75% of the articles using them, then the hot plate in almost 61%, the cold test in 30%, and coming at last, the use of pin pricking maneuver in 4% of the papers (23-153). As a resume, the most common variable measured was the mechanical stimuli; after that, the thermic response and finally, the mechanical function. Our investigation found many other techniques to evaluate pain. We have described them in this article as a

miscellaneous group. To acknowledge all the different methodologies, we included them in table 3.

This shift of paradigms allows us to identify which are the main tests used in the selected articles. Therefore, this must help to standardize the pain measures in the next scientific productions regarding this field.

Conclusion

Neuropathic pain can be produced with a constriction model of the sciatic nerve, known as the Bennett technique. For successfully recreating this procedure, the correct equipment and set of steps described should be followed. The Von Frey filament test is one of the most effective ways of measuring painful stimuli in rat extremities. The pin pricking test, cold score, and hot-plate test are complementary methods that might help to understand more specifically how rats react to algogenic stimuli. Furthermore, some other experiments use different methods to measure neuropathic pain after sciatic nerve compression in rats.

Acknowledgments

The authors would like to thank Universidad Anahuac, the Stereotactic and Functional Neurosurgery Unit of Hospital General de México "Dr. Eduardo Liceaga", and the Alpha Health Sciences Leadership Program, for all their support in realizing this manuscript.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that the procedures followed complied with the ethical standards of the responsible human and animal experimentation committee and adhered to the World Medical Association and the Declaration of Helsinki. The procedures were approved by the institutional Ethics Committee.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161:1976-82.
2. González-Hermosillo DC, González-Hermosillo LM, Villaseñor-Almaraz M, Ballesteros-Herrera D, Moreno-Jiménez S, Corona-Cedillo R, et al. Current concepts of pain pathways: a brief review of anatomy, physiology, and medical imaging. Curr Med Imaging. 2023;20:e190523217114. doi: 10.2174/1573405620666230519144112..
3. García-Jeronimo AI, Armas-Salazar A, García-Muñoz L, Navarro-Olvera JL, Esqueda-Liquidano MA, Carrillo-Ruiz JD. Neuropathic pain and positive sensory symptoms in brachial plexus neuropathy: an exploratory study of outcomes after surgical decompression and proposal of a new sensory frequency of symptoms scale. J Integr Neurosci. 2023;22:25.
4. McMackin MZ, Lewin MR, Tabuena DR, Arreola FE, Moffatt C, Fuse M. Use of von Frey filaments to assess nociceptive sensitization in the hornworm, *Manduca sexta*. J Neurosci Methods. 2016;257:139-46.
5. Campana G, Rimondini R. Mechanical nociception in mice and rats: measurement with automated von Frey equipment. Methods Mol Biol. 2021;2201:195-8.
6. Vranken JH. Elucidation of pathophysiology and treatment of neuropathic pain. Cent Nerv Syst Agents Med Chem. 2012;12:304-14.
7. Bennett GJ, Xie YK. A peripheral mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain. 1988;33:87-107.
8. Bennett GJ, Chung JM, Honore M, Seltzer ZE. Models of neuropathic pain in the rat. Curr Protoc Neurosci. 2003;22:9-14.
9. Suzuki K, Baad-Hansen L, Svensson P. Verbal instructions influence pain thresholds assessment: a study using manual and electronic mechanical stimulators. Eur J Pain. 2017;21:900-6.
10. Deuis JR, Dvorakova LS, Vetter I. Methods used to evaluate pain behaviors in rodents. Front Molecul Neurosci. 2017;10:284.
11. Kim SH, Chung JM. An experimental model for peripheral neuropathy produced by segmental spinal nerve ligation in the rat. Pain. 1992;50:355-63.
12. Scholz J, Broom DC, Youn DH, Mills CD, Kohno T, Suter MR, et al. Blocking caspase activity prevents transsynaptic neuronal apoptosis and the loss of inhibition in lamina II of the dorsal horn after peripheral nerve injury. J Neurosci. 2005;25:7317-23.
13. Chaplan SR, Bach FW, Pogrel JW, Chung JM, Yaksh TL. Quantitative assessment of tactile allodynia in the rat paw. J Neurosci Methods. 1994;53:55-6.
14. Gonzalez-Cano R, Boivin B, Bullock D, Cornelissen L, Andrews N, Costigan M. Up-down reader: an open-source program for efficiently processing 50% von Frey thresholds. Front Pharmacol. 2018;9:433.
15. Kingery WS, Vallin JA. The development of chronic mechanical hyperalgesia, autotomy and collateral sprouting following sciatic nerve section in rat. Pain. 1989;38:321-32.
16. Kingery WS, Lu JD, Roffers JA, Kell DR. The resolution of neuropathic hyperalgesia following motor and sensory functional recovery in sciatic axonotmetic mononeuropathies. Pain. 1994;58:157-68.
17. Hao JX, Xu IS, Xu XJ, Wiesenfeld-Hallin Z. Effects of intrathecal morphine, clonidine and baclofen on allodynia after partial sciatic nerve injury in the rat. Acta Anaesthesiol Scand. 1999;43:1027-34.
18. Hao JX, Shi TJ, Xu IS, Kaupilla T, Xu XJ, Hökfelt T, Bartfai T, Wiesenfeld-Hallin Z. Intrathecal galanin alleviates allodynia-like behaviour in rats after partial peripheral nerve injury. Eur J Neurosci. 1999; 11(2):427-32.
19. Woolfe G, MacDonald AD. The evaluation of the analgesic action of pethidine hydrochloride (Demerol). JPET. 1944;80:300-7.
20. Du J, Deng Y, Qiu Z, Sun G, Guo Y, Hei Z, et al. Curcumin alleviates chronic pain and improves cognitive impairment via enhancing hippocampal neurogenesis in sciatic nerve constriction rats. J Pain Res. 2021;14:1061-70.
21. Abed AR, Abed A, Banafshe HR, Malekabad ES, Gorgani-Firuzjaee S, Dadashi AR. Effect of biotin supplementation on neuropathic pain induced by chronic constriction of the sciatic nerve in the rat. Res Pharm Sci. 2021;16:250.
22. D'Amour FE, Smith DL. A method for determining loss of pain sensation. J Pharmacol Exp Ther. 1941;72:74-9.
23. Hargreaves K, Dubner R, Brown F, Flores C, Joris J. A new and sensitive method for measuring thermal nociception incutaneous hyperalgesia. Pain. 1988;32:77-88.

Revista Médica del
Hospital General de México

PERMANYER

Check for updates

ORIGINAL ARTICLE

Auditory brainstem response thresholds difference using Click and CE-Chirp in auditory brainstem response

Emilio Dávalos[1], Jesús A. Silva-Rojas[1], and Pablo A. Ysunza[2]*

[1]Audiology, Otoneurology and Phoniatrics Service, Physical Medicine and Rehabilitation Unit 601, Hospital General de México Dr. Eduardo Liceaga, Secretaría de Salud, Mexico City, Mexico; [2]Ian Jackson Clet Palate and Craniofacial Clinic, Neuroscience Program, Beaumont Health, Royal Oak, MI, U.S.A.

Abstract

Introduction: *Auditory Brainstem Response, also known as short-latency auditory evoked potentials (SLAEP) is a useful tool for performing auditory evaluations in children and difficult to test patients. Different types of stimuli have been described to elicit the auditory response including Click and CE-chirps among others.* **Objective:** *The objective the study is to compare the auditory brainstem response thresholds obtained with Click and CE-Chirp stimuli and to describe if there is a difference in the correction factor for the auditory brainstem hearing threshold between the two stimuli.* **Material and methods:** *A retrospective, cross-sectional, observational, comparative, and descriptive study was carried out. The patients' records who, as a diagnostic protocol, had been evaluated with auditory brainstem response with both Click and CE-Chirp, were analyzed. 38 ears were reviewed with both CE-Chirp and Click recordings. The mean and standard deviations between the electrophysiological hearing thresholds of both stimuli were calculated. A student's t-test was performed between the means of the hearing threshold. The correction factor for CE-Chirp was calculated.* **Results:** *The means of the electrophysiological hearing threshold obtained with Click stimulus were of 30.26 dBnHL and with CE-Chirp of 23.21 dBnHL. There is a significant difference between the hearing thresholds obtained with both stimuli with p = 0.000.* **Conclusions:** *The threshold difference between CE-Chirp and Click was 6.57 dB, and the thresholds obtained with CE-Chirp are lower than with Click. Therefore, thresholds between 20 dBnHL and 25 dBNHL with CE Chirp should be considered normal, unlike the Click that is universally accepted as normal with 30 dBnHL or less.*

Keywords: *Auditory brainstem response. CE-Chirp stimuli. Click stimuli. Hearing threshold.*

Introduction

Short-latency auditory evoked potentials (SLAEP) are defined as the bioelectrical response recorded in the scalp after the activation of the fibers of the auditory pathway (from the auditory nerve to the inferior colliculus), and this response consists of a sequence of up to seven positive waves toward the vertex recorded by specialized electrophysiological equipment. The waves are usually labeled with Roman numerals of which waves I, III, and V are the most important and specifically, the V wave is used to determine the electrophysiological auditory threshold[1,2].

The study can identify the presence of hearing loss in subjects who cannot cooperate for audiometry, either because of their age, such as neonates, or adults with inability to participate, such as dementia. The test itself is a fairly objective measure of the measurement of electrophysiological auditory thresholds and is considered to be a reliable and very approximate estimate of behavioral thresholds at frequencies from 2000 to 4000 Hz[2].

The auditory threshold of the SLAEP obtained with Click stimulus is obtained with the lowest stimulus intensity at which the V-wave can be identified in a clear

***Correspondence:**
Emilio Dávalos
E-mail: emidavagp@gmail.com

Date of reception: 21-02-2024
Date of acceptance: 24-07-2024
DOI: 10.24875/HGMX.24000016

Available online: 01-04-2025
Rev Med Hosp Gen Mex. 2025;88(2):74-79
www.hospitalgeneral.mx

and reproducible way. It provides a fairly close estimate of the behavioral hearing threshold and is considered the gold standard for determining the hearing threshold in non-cooperative patients. However, for decades, it has been known that the electrophysiological auditory threshold obtained with Click is higher than the behavioral threshold obtained, for example, with tonal audiometry, with a difference between behavioral thresholds and electrophysiological thresholds with Click of approximately 10 dB[3].

The Click stimulus is a broadband stimulus, that is, it stimulates many cochlear frequencies and has been used routinely in SLAEP for more than five decades[4]. The Click is a stimulus produced by a square wave electrical pulse lasting 100 μs. It allows the stimulation of the entire cochlea; however, this Click causes a progressive stimulation from high to low frequencies, that is, it does not stimulate them simultaneously, which produces a depolarization out of phase in time of the axons of the auditory nerve. This implies a limitation when obtaining records because we only obtain responses from the base of the cochlea, more specifically frequencies between 2000 Hz and 6000 Hz, excluding frequencies below 2000 Hz that are stimulated later than those mentioned above.

Similarly, the CE-Chirp stimulus is also a broadband stimulus that also allows the activation of the entire cochlea, however, in contrast, because it is designed to avoid the lag in the high and low frequencies, a synchronized depolarization of a greater number of axonal fibers is obtained, which produces a bioelectric vector of greater amplitude and this results in larger waves, including the V wave, in addition to having a wider frequency contribution, from 250 Hz to 8000 Hz. It was designed by Klaus Elberling in 2007 due to the limitations in frequency stimulation offered by the Click stimulus[4-6]. It is assumed that a more robust bioelectrical vector produces larger SLAEP waves and at lower stimulation intensities with the CE-Chirp.

Due to the potential difference between the auditory thresholds obtained by Click and CE-Chirp, there is a need to measure the difference between the thresholds obtained with both stimuli and thus avoid diagnostic errors and the appropriate classification of hearing loss according to the degree of loss. Since it is commonly used that when viewing V wave at 30 dBnHL with Click, the study is stopped and it is considered normal hearing[7].

There are previous studies in which SLAEP are compared using Click stimulus and CE-Chirp stimulus; however, they compare other parameters other than the threshold such as the absolute latencies of waves I, III, and V, the interlatency intervals, the amplitude of the V and I waves, and the interaural difference of the V waves between the 2 stimuli finding similar values between the two stimuli; however, they do not specifically compare the difference in V-wave thresholds obtained with CE-Chirp and Click[8]. Other studies have reported differences between audiometric thresholds and SLAEP thresholds with Click[9-11].

Studies have also been carried out where auditory thresholds are compared using different stimuli in the SLAEP, such as tone burst, tone pip, NB-Chirp[12-17] which are specific frequency stimuli. Whose usefulness is restricted to determining hearing by frequency, however, the performance of SLAEP with these stimuli considerably increases the time of performance of the test and limits its use to patients with hearing loss confirmed by CE-Chirp or Click, in whom more information is necessary by frequency, for example for an adequate adaptation of hearing aids. However, the most frequently used and universally used stimuli are the CE-Chirp and the Click, which allow tests to be carried out more quickly to identify normal hearing and hearing loss in the first stage[18].

To our knowledge, there is a study with 10 adult participants (20 ears) with normal hearing, the responses of the SLAEP using the CE-Chirp stimulus and Click stimulus were compared with the auditory thresholds obtained by tonal audiometry, it was found that when the CE-Chirp stimulus was used, the V-wave thresholds are closer to the audiometric thresholds, with a difference of 2 decibels between CE-Chirp and tonal audiometry. However, the sample is very small and the sample is restricted to adults, not including pediatric patients and patients with hearing loss[19,20].

The purpose of this study is to determine what is the difference in decibels between the auditory thresholds obtained with SLAEP with CE-Chirp and the auditory thresholds obtained with Click in the same ears of patients who represent the tertiary hospital population with a spectrum of patients more representative of a specialized hospital service such as ours. Including mostly children who are the ones who are most frequently subjected to SLAEP to determine threshold[20].

Material and methods

A retrospective, cross-sectional, observational, comparative, and descriptive study was conducted. Clinical records of the Audiology, Otoneurology, and Phoniatrics service of the Hospital General de México were

reviewed with a graphic report of auditory evoked potentials of short latency belonging to norm hearing or hearing-impaired patients who attended diagnostic evaluation with the interacoustic device model Eclipse EP 25 and that as a diagnostic protocol, they were evaluated with both stimuli, CE-Chirp and Click. The final sample size was 38 ears (19 patients) as explained below.

As a diagnostic protocol, clinical records were reviewed in which the SLAEP was performed on the patients according to the conventional preparation with the following methodology: patients who attended with wakefulness were positioned in the supine position, entering physiological sleep at the beginning of the study, after preparing the patient and placing electrodes, with ER-3A insertion hearing aids. Impedance measurement < 5 Ohms, the stimulation rates were preserved according to how the equipment is programmed from the factory: with Click stimulus at a stimulus presentation rate of 33.1/s and subsequently records with CE-Chirp of 45.1/s, in both cases of alternating polarity. No moving the insertion hearing aids or electrodes during the study.

A total of 300 patient records with CALAP records were reviewed, which included 572 ears, of which 534 ears were excluded because the CALP records presented different situations that influenced their exclusion, such as poor morphology and irregular replicability and patients with central auditory pathology, records with only one type of stimulus, presence of noise, etc. A total of 38 ears, 22 right ears, and 16 left ears were selected that had good quality SLAEP recordings with both Click and CE-Chirp, with replication at all intensities with threshold search up to the lowest possible intensities and that both recordings were made during the same session (Fig. 1).

The electrophysiological auditory threshold was defined as the lowest audiological level at which a clear V-wave response was observed for each of the stimuli, CE-Chirp and Click. The aim was for the recordings to have a lower intensity register than the V-wave detection to ensure that at lower intensities the V-wave was no longer identified in both stimuli. The electrophysiological auditory thresholds of the CE-Chirp and Click stimuli were compared in the same ear. The data obtained were analyzed in the SPSS software version 28.0 (IBM Inc.).

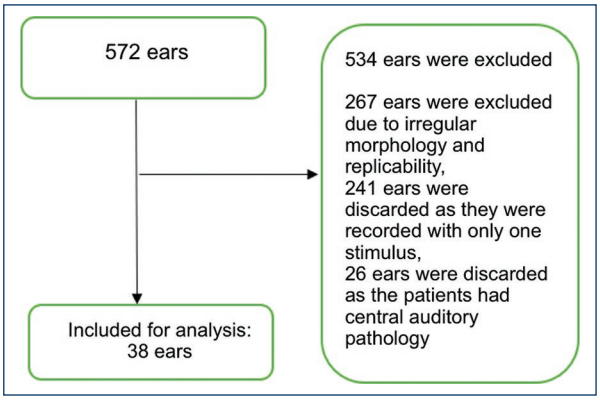


Figure 1. The total number of ears tested, the number of ears excluded for different issues (as described in the figure), and the total number of ears used for the analysis are displayed.

Results

17 patients were male and 6 females, the average age was 2 years 8 months. The age range was from 1 month of life to 24 years (Table 1). Eight ears have the diagnosis of hearing loss and 30 ears have normal hearing. The mean electrophysiological auditory threshold obtained with Click stimulus was 30.26 dBnHL with a standard deviation of 20.5 dBnHL. The mean electrophysiological auditory threshold obtained with CE-Chirp stimulus was 23.21 dBnHL with a standard deviation of 19.7 dBnHL. The standard deviations of the electrophysiological auditory thresholds obtained were wide since normal hearing patients and those with hearing loss were included (Table 2 and Fig. 2). The fact that the standard deviations are so wide is to be expected, since patients with normal hearing and with different degrees of hearing loss were included so that the sample of patients was representative of the patients in our department. It was decided to include real patients from a broader spectrum since there is, as mentioned, only one study in normal adults. One objective is to see the behavior of the test with real patients[20].

A t-test of paired samples was performed comparing the means of the electrophysiological auditory thresholds of both stimuli to determine the existence of statistical differences in the means of the thresholds obtained by CE-Chirp and Click in each ear, finding p = 0.000 in all cases (total and per ear), which allows us to conclude that the difference between the means is reliable. The results in the right ears were 5682 dB, in the left ears were 7813 dB and the total of 6579 dB always with higher thresholds for the Click. Figure 3 shows the comparison of recordings in one ear of the same patient with normal hearing using Click and CE-Chirp in which a difference of 10 dB nHL between both recordings can be observed.

Table 1. The age range, sex, and hearing of the subjects used for analysis are displayed

Age range (months)	No. patients	Male	Female	Hearing hearing loss	Norm-hearing
1-6	13	11	2	2	11
7-12	4	4	0	1	3
13-24	1	1	0	0	1
2-24 years	5	1	4	3	2
Total	23	17	6	6	17

Table 2. Electrophysiological auditory thresholds obtained with Click stimulus and CE-Chirp stimulus by ear and total. Means of electrophysiological auditory thresholds obtained per ear with standard deviation

Stimulus	Minimum hearing threshold (dB)	Maximum hearing threshold (dB)	Media (dB)	Standard deviation (dB)
Click right ear	10	65	26.82	14.355
Click left ear	15	90	35.00	26.646
Total Click	10	90	30.26	20.532
CE-Chirp right ear	10	60	21.14	14.387
CE-Chirp left ear	5	85	25.50	24.597
Total CE-Chirp	5	85	23.21	19.780

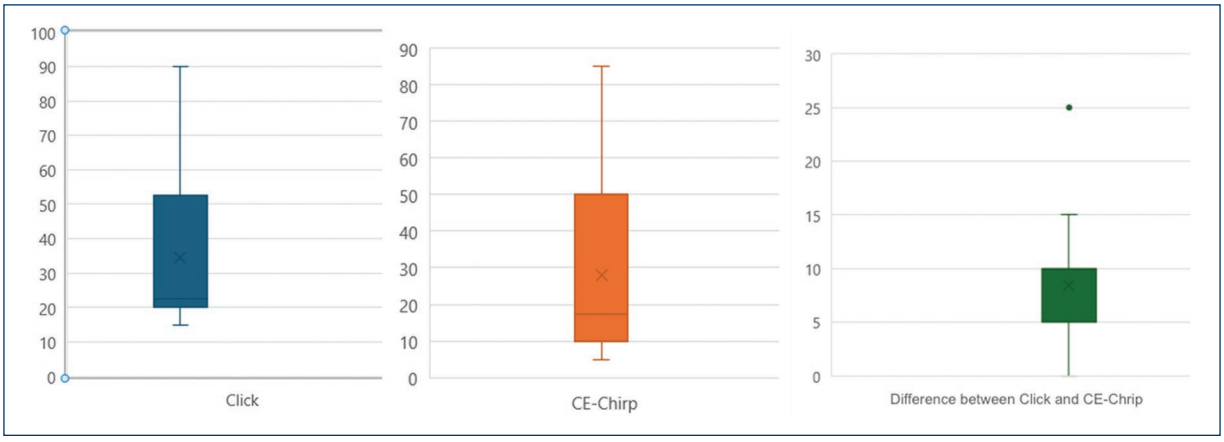


Figure 2. Auditory threshold with Click in blue, with CE-Chirp in orange, difference between the auditory threshold using both stimuli in green, all of the above in dB.

Due to the non-normal distribution and the sample is relatively small, a Wilcoxon test was also performed, since it is a paired sample, also finding a p = 0.

Discussion

According to the results obtained, the difference in the thresholds of SLAEP obtained with CE-Chirp and Click is 6.57 dB, which clearly indicates that the thresholds obtained with CE-Chirp are better than the thresholds obtained with Click; therefore, we propose that to consider the normal threshold of V-wave with CE-Chirp, they should be obtained in a limit between 20 dBnHL and 25 dbNHL. We preferably suggest 20 dBnHL to have a little more specificity and thus avoid false negatives. As mentioned with the Click universally, and for

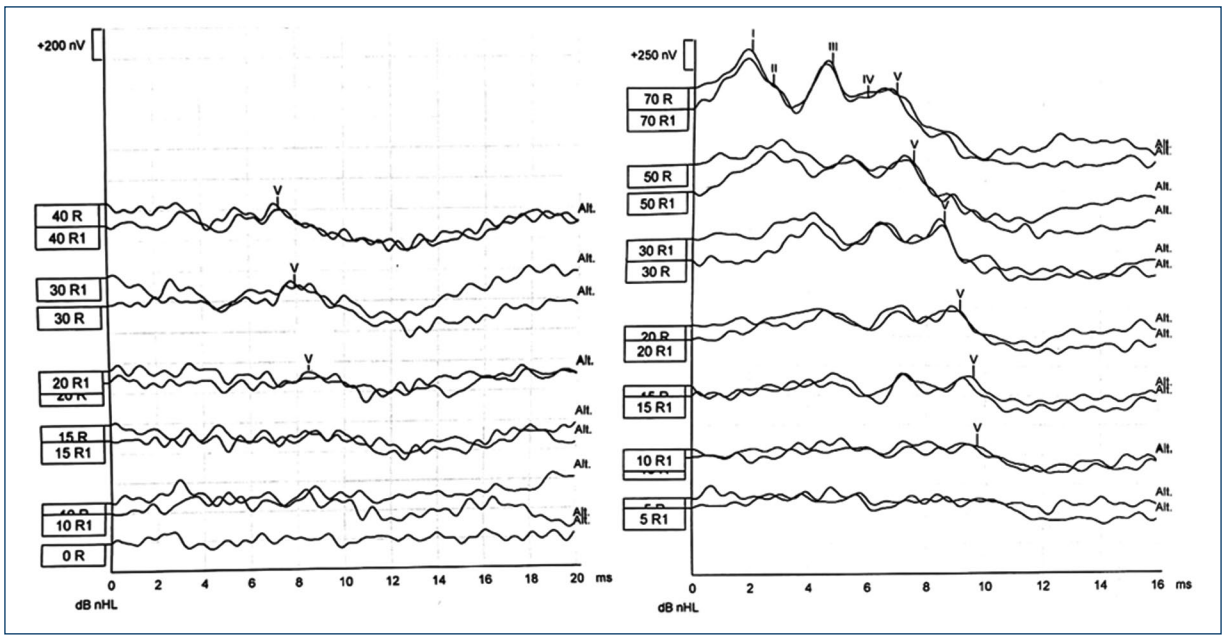


Figure 3. Short-latency auditory evoked potentials of the right ear of a patient with normal hearing using CE-Chirp stimulus on the right side and Click on the left side. A better threshold is observed with CE-Chirp by 10 dBnHL.

decades, the limit of the normal threshold has been considered equal to 30 dBnHL. In our case, we suggest that with CE-Chirp, it is 20 dBnHL. With this correction, we will prevent patients with superficial hearing loss from being misdiagnosed as normal when using CE-Chirp.

The Click stimulus has been used for at least 5 decades or more and there is extensive knowledge of its behavior in SLAEP. However, because the CE-Chirp is more recent (2007), there is less evidence of its electrophysiological performance both for the measurement of auditory thresholds and evaluation of neurophysiological dysfunction. As mentioned, the CE-Chirp will cause a more robust V-wave response to lower the hearing threshold, which is what this study has intended to answer. Moreover, in this way, we would avoid misclassifying the degrees of hearing loss and/or normal hearing and consequently the subsequent management. The results are consistent with the only study in normal adults mentioned above[19].

There are limitations for this study. The number of ears included in the sample is reduced. Moreover, the characteristics of the patients are heterogeneous. Ears with normal hearing, and ears with different degrees of hearing loss were included in the sample. Although most of them were pediatric, there were also X adults. It is necessary to mention that despite this, the behavior of the test was very similar to that obtained in normal adult patients[19]; however, we know that different types and degrees of hearing loss could influence the results. Therefore, we suggest continuing this line of research to evaluate in prospective studies the performance of SLAEP with EC-Chirp in different degrees and types of hearing loss, stratified by age group, as was done in the past with the Click.

Conclusion

This study found different electrophysiological auditory thresholds in the same ears of the same patients with 2 different broadband stimuli, Click and CE-Chirp, which are by far the most universally used. Based on our findings, it is recommended that when determining the hearing threshold in SLAEP with CE-Chirp, a threshold of 20 dBnHL should be considered normal and not 30 dBnHL used with the Click. In this way, errors in the diagnosis, follow-up and management of patients are avoided.

Acknowledgments

The authors would like to thank at Drs. D. Ortiz-Morales and L. Reyes-Contreras.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human and animal subjects. The authors state that no experiments were conducted on humans or animals for this study.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript.

References

1. Eggermont JJ. Auditory brainstem response. In: Levin KH, Chauvel P, editors. Handbook of Clinical Neurology. 1st ed. Amsterdam, NL: Elsevier; 2019. p. 451-64.
2. Habib SH, Habib SS. Auditory brainstem response: an overview of neurophysiological implications and clinical applications - a narrative review. J Pak Med Assoc. 2021;71:2230-6.
3. Sininger YS. Auditory brain stem response for objective measures of hearing. Ear Hear. 1993;14:23-30.
4. Kaynakoğlu B, Ceyhan S. Which stimulus should be used for auditory brainstem response in newborns; CE-Chirp® level specific versus click stimulus. Int J Pediatr Otorhinolaryngol. 2023;170:111597.
5. Rouillon I, Parodi M, Denoyelle F, Loundon N. How to perform ABR in young children. Eur Ann Otorhinolaryngol Head Neck Dis. 2016;133:431-5.
6. Bargen GA. Chirp-evoked auditory brainstem response in children: a review. Am J Audiol. 2015;24:573-83.
7. Smith JT, Wolfe J. Using contemporary ABR protocols to get accurate results. Hear J. 2014;67:36, 38-40.
8. Cargnelutti M, Cóser PL, Biaggio EPV. LS CE-Chirp® vs. Click in the neuroaudiological diagnosis by ABR. Braz J Otorhinolaryngol. 2017; 83:313-7.
9. McCreery RW, Kaminski J, Beauchaine K, Lenzen N, Simms K, Gorga MP. The impact of degree of hearing loss on auditory brainstem response predictions of behavioral thresholds. Ear Hear. 2015;36:309-19.
10. Li Z, Lai X, Lai J, Qi M, Yuan L, Zeng X, et al. Correction of the estimated hearing level of NB Chirp ABR in normal hearing population. Audiol Neurootol. 2022;27:388-96.
11. Stapells DR, Gravel JS, Martin BA. Thresholds for auditory brain stem responses to tones in notched noise from infants and young children with normal hearing or sensorineural hearing loss. Ear Hear. 1995;16:361-71.
12. Stapells D. Threshold estimation by the tone -evoked auditory brainstem response: a literature meta-analysis. J Speech Lang Pathol Audiol. 2000;24:74-82.
13. Ferm I, Lightfoot G. Further comparisons of ABR response amplitudes, test time, and estimation of hearing threshold using frequency-specific chirp and tone pip stimuli in newborns: findings at 0.5 and 2 kHz. Int J Audiol. 2015;54:745-50.
14. Gøtsche-Rasmussen K, Poulsen T, Elberling C. Reference hearing threshold levels for chirp signals delivered by an ER-3A insert earphone. Int J Audiol. 2012;51:794-9.
15. British Society of Audiology. Guidelines for the Early Audiological Assessment and Management of Babies Referred from the Newborn Hearing Screening Programme. United Kingdom: British Society of Audiology; 2021. p. 1-52.
16. Ferm I, Lightfoot G, Stevens J. Comparison of ABR response amplitude, test time, and estimation of hearing threshold using frequency specific chirp and tone pip stimuli in newborns. Int J Audiol. 2013;52:419-23.
17. Bell SL, Allen R, Lutman ME. An investigation of the use of band-limited chirp stimuli to obtain the auditory brainstem response. Int J Audiol. 2002;41:271-8.
18. Biagio-de Jager L, van Dyk Z, Vinck BH. Diagnostic accuracy of CE Chirp. Int J Pediatr Otorhinolaryngol. 2020;135:110071.
19. El Kousht M, El Minawy M, El Dessouky T, Koura R, Essam M. The sensitivity of the CE-Chirp auditory brainstem response in estimating hearing thresholds in different audiometric configurations. Egypt J Otolaryngol. 2019;35:56-62.
20. Nierenberg AA, Feinstein AR. How to evaluate a diagnostic marker test. Lessons from the rise and fall of dexamethasone suppression test. JAMA. 1988;259:1699-702.

Revista Médica del
Hospital General de México

PERMANYER

Check for updates

REVIEW ARTICLE

Hypoxic-ischemic brain injury: literature review

Jésser M. Herrera-Salgado[1,2], Luis E. Reyes-Mendoza[2], Jesús C. Briones-Garduño[3], and Sindy A. Gutiérrez-Chavarría[4]*

[1]Obstetric Intensive Care Unit, Military Hospital for Women's Specialties and Neonatology; [2]Coordination of Medical Education and Research, Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE). Mexico City; [3]Department of Scientific Research, Hospital Materno Perinatal Mónica Pretelini Sáenz, Toluca de Lerdo, State of Mexico; [4]Internal Medicine, Hematology, Bone Marrow Cell Transplant Service, ISSSTE, Mexico City. Mexico

Abstract

Hypoxic-ischemic brain injury refers to the pathophysiological consequence of deprivation of adequate cerebral perfusion that occurs transiently. This medical complication is commonly related to an event of cardiac arrest (CA), respiratory failure, incidents of near drowning, and different states of shock that could trigger severe hypoperfusion and its pathological sequelae. The consequences of this clinical entity can vary from almost complete recovery to brain death. Treatment is based on correcting the cause of hypoperfusion, adequate neurocritical care, and in survivors, multidisciplinary rehabilitation involving not only the patient but family and caregivers. In this manuscript, we reviewed recent literature with the aim of understanding and making known the appropriate approach to this complication. A search was conducted for recent literature on the topic mentioned using the keywords "Hypoxic-ischemic brain injury, Hypoxic-ischemic encephalopathy in adults" in the database PubMed of the National Center for Biotechnology Information. The search resulted in 62 articles, the search was delimited with the temporality from 2015 to 2023, 20 were selected, considering those that can be integrated into the themes that make up the structure, that had as references recent literature < 10 years old; those that had information not directly related to the topic or that did not include the subsections to be addressed in the review were not included.

Keywords: *Hypoxic-ischemic brain injury. Anoxic encephalopathy. Anoxic brain injury.*

Introduction

Hypoxic-ischemic brain injury (HIBI) is a serious medical condition that can have severe consequences on an individual's cognitive, motor, and sensory functions[1]. HIBI commonly occurs due to a variety of reasons, including cardiac arrest (CA), respiratory failure, near-drowning incidents, severe blood loss, and complications during childbirth. When the brain is deprived of oxygen and nutrients for an extended period, it can result in significant cellular damage and even cell death. However, some advances are being made in this area, and there is a focus on identifying patients with the prospect of improving neurologic morbidity and mortality[2], usually intubated and have a history of prolonged resuscitation due to several diagnoses[1,2].

The severity and extent of HIBI depend on various factors, such as the duration and severity of the oxygen deprivation, the age and overall health of the affected individual, and the promptness and effectiveness of medical intervention. In the United States, approximately 180.000-450.000 people (in Europe about 270.000 people) are dying due to sudden cardiac death per year[3].

Diagnostic imaging techniques are essential for a proper evaluation while anoxia is a common cause of

***Correspondence:**
Jésser M. Herrera-Salgado
E-mail: drjherrera@gmail.com

Date of reception: 17-01-2024
Date of acceptance: 01-07-2024
DOI: 10.24875/HGMX.24000010

Available online: 21-11-2024
Rev Med Hosp Gen Mex. 2025;88(2):80-87
www.hospitalgeneral.mx

diffuse cortical and subcortical restricted diffusion, this neuroimaging pattern of brain injury can be observed in a variety of other central nervous system and systemic conditions of varying pathophysiology, severity, and long-term prognosis[4]. Recovery from HIBI varies significantly among individuals and depends on the extent of brain damage. Some individuals may experience partial or complete recovery, while others may require long-term rehabilitation and support to regain lost functions and improve their quality of life. Ongoing research aims to develop new treatments and interventions to enhance the outcomes of individuals with HIBI. Early recognition, timely medical intervention, and rehabilitation efforts play a vital role in optimizing the prognosis for individuals affected by HIBI[1-3]. In this manuscript, we present recent literature with the aim of understanding and making known the appropriate approach to this complication.

Epidemiology

Hypoxic-ischemic cerebral injury occurs at any age, although the etiology is significantly different[1-4]. Although surveillance of statistics regarding CA and the neurologic outcome is varied, further studies are needed to determine the differences between in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA). Cardiac diseases are the main cause of CAs (82.4%) and subsequent brain damage. In the United States, approximately 180.000-450.000 people (in Europe about 270,000 people) are dying due to sudden cardiac death per year[3]. In a series of clinical cases reported, the following results were found within the most important etiologies: cardiac infarction (30.1%), cardiac arrhythmia (4.3%), pulmonary embolism (4.3%), respiratory insufficiency (3.2%), attempted suicide (3.2%), Qt syndrome (2.2%), heart injuries (2.2%), intoxication (2.2%), anaphylactic, shock (1.1%), status epilepticus (1.1%), unknown (24.7%), and other cause (21.5%)[3]. The spectrum of disability resulting from HIBI ranges from complete recovery to coma or even death. Clinical trials showed that 27% of post-hypoxic coma patients regained consciousness within 28 days, 9% remained comatose or in an unresponsive wakefulness syndrome (UWS), and 64% died. In another prospective clinical study, 18.6% of patients stayed in an UWS. Hypoxic-ischemic injury is the most common cause of death in patients who initially survive CA[3,4].

The worldwide prevalence of stroke in 2010 was 33 million, with 16.9 million people having a first stroke, of which 795,000 were American and 1.1 million European. It has been estimated that approximately one-third of people fail to regain upper limb capacity, despite receiving therapy. This has important implications for both individuals and the wider society as reduced upper limb function is associated with dependence and poor quality of life for both patients and carers and impacts on national economies. The incidence rate of HIBI secondary to stroke in Europe is about 235/100,000 population. Outcome data among European countries are very heterogeneous[5].

Definition

It is a syndrome characterized by motor and neuropsychological sequelae secondary to low cerebral blood flow (CBF) and a decrease in arterial oxygen concentration that leads to a loss of cerebral vascular autoregulation and subsequently diffuse brain damage[1-5]. The severity of the injuries correlates with the duration of oxygen deprivation, and it is estimated that after 4-5 min of anoxia, the lesions are irreversible. Clinical trials showed that 27% of post-hypoxic coma patients regained consciousness within 28 days, 9% remained comatose or in an UWS, and 64% died[6,7].

Diagnosis

Medical history

When performing the initial evaluation it musts take a detailed medical history, including information about the circumstances leading to the suspected HIBI, such as CA, near drowning, or respiratory distress. It is essential to differentiate the clinical scenarios of IHCA from OHCA because the prognosis is totally different[6]. In the context of the OHCA patient, the circumstances of the CA event, exposure to substances, and chronic and degenerative history must be estimated as precisely as possible, specifying the time that the patient was in impaired alertness and without medical or paramedical assistance.

In the IHCA patient, we must be exhaustive in identifying the triggering cause and correcting it as precisely as possible, as well as establishing the necessary critical care, aimed at correcting the pathophysiology involved in the trigger.

Physical examination

It is necessary to assess neurological function, motor abilities, reflexes, sensory responses, and other signs

of brain injury, and do it several times. One of the most important parts of the clinical assessment is determining whether the patient's examination is reliable, or whether it is confounded by the administration of medications. Even medications that are no longer being given, but were administered within the previous few days could still be confounding the examination. Any estimation of prognosis must be delayed until a reliable examination, free of the effects of recent sedatives/analgesics or metabolic abnormalities, is obtained. Not uncommonly, these patients are suffering from multiorgan failure with cardiogenic shock, acute kidney injury, and shock liver. Opioids and benzodiazepines are liberally administered, especially early, and these may need 3-5 days to clear once stopped, particularly in the setting of kidney or liver dysfunction[7].

Various syndromes are integrated in relation to alterations in the state of consciousness:

akinetic mutism is characterized by the fact that the individual retains his or her waking state, without response to any type of stimulus, and with the absence of spasticity or abnormal reflexes, that is, the cortical-spinal pathways are intact.

Induced or iatrogenic coma

It is a state similar to coma, produced by the administration of drugs or substances that reduce metabolism and cerebral flow, favoring the loss of brain stem functions.

Obtundation

Moderate disturbance of wakefulness in which attention is focused on a fixed point.

Stupor

In this state, there is a loss of verbal command-type responses, but retains an adequate reaction to painful stimuli, accompanied by the ability to discriminate the painful point.

Drowsiness

It is characterized by the tendency to sleep in which the adequate response to simple and complex verbal commands, and painful stimuli, is preserved. This mental state is characterized by decreased comprehension, coherence, and the ability to reason.

Locked in syndrome

It consists of a focal lesion of the ventral pons that is clinically characterized by quadriplegia and anarthria, preservation of the level of wakefulness and the content of consciousness, as well as vertical eye movements and blinking. It is not an alteration of the state of consciousness, but it can be confused with them.

Coma

It comes from the Greek "Koma" which means deep sleep. This state is characterized by the total absence of wakefulness and persistent content of consciousness (greater than an hour to differentiate it from transient states). It includes states in which there is a loss of consciousness itself, of relationships, and of the phenomenon of awakening.

Vegetative state

This state is characterized by the recovery of the waking state accompanied by the maintenance of the complete loss of consciousness content after a coma[1]. In general, the cardiorespiratory functions and the functionality of the cranial nerves are intact.

State of minimal consciousness

It is a state where there are global alterations of consciousness with elements of wakefulness, that is, there is intermittent evidence of awareness of oneself or the environment.

Electroencephalogram (EEG)

The acute form of encephalopathy can range from mild confusion and delirium to coma. In the more chronic, slowly progressive, or static conditions of encephalopathy, there may be retention of attention initially with loss of cognitive capacity. EEG helps evaluate patients with acute and chronic encephalopathies. The primary role is in differentiating the conditions associated with seizures[7].

In comatose individuals, diffuse α frequency activity can be seen. When the predominant α activity is noted in the posterior head regions and varies with noxious external stimuli, the etiology of the coma may be secondary to a brainstem lesion; this is associated with a poor prognosis. More diffuse α activity with less reactivity to external stimuli is seen in anoxic injury after CA and is commonly associated with a poor prognosis.

When α coma is noted on EEG, the overall outcome depends on the etiology and reactivity to external stimuli, with a better prognosis in toxic encephalopathies and worse in anoxic encephalopathies. Spindle coma consists of paroxysmal bursts of 11-14 Hz activity appearing on a δ background and is usually known to occur in cases of anoxic injury, intracranial hemorrhage, diffuse cerebral insults, and head trauma. EEG pattern spindle coma is associated with the involvement of the pontomesencephalic junction[3].

Summarizing: Anoxic or hypoxic injury is encountered in CA, and the extent of brain injury correlates with the severity of anoxia. This includes a wide spectrum from mild, slowing to severe suppression. Poor prognostic EEG findings include α or spindle coma with poor reactivity, burst suppression pattern with longer interburst intervals, and electrocerebral inactivity or silence (Figs. 1 and 2).

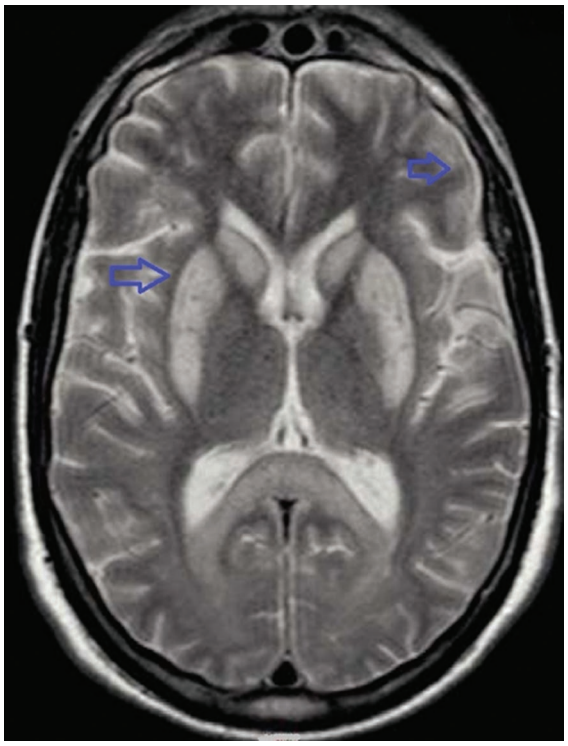


Figure 1. Magnetic resonance imaging axial section in T2 sequence highlights hyperintensity in basal ganglia and dedifferentiation of white and gray matter.

Serum biomarkers

Biomarkers can help to identify whether patients have a biological predisposition to respond to a particular therapy. Following hypoxic brain injury, biomarkers are released in the blood and cerebrospinal fluid (CSF) (like Neuron-specific enolase [NSE], S100β, miRNA, etc.), which can be used for prognostication and management purpose[6,8]. However, a clinical trial explorative analysis showed that early burden of cerebral hypoxia, but not hyperoxia was significantly associated with low brain electrical activity and severe intracranial hemorrhage while none of the blood biomarkers were associated with the burden of either cerebral hypo- or hyperoxia[6,8].

Here are some important diagnostic and prognostic biomarkers:

NSE: NSE is also known as gamma-enolase or enolase 2 (encoded by ENO2 gene). NSE exists as a homodimer in mature neurons and neuroendocrine cells. NSE elevations in the blood compartment have been documented in severe HIBI secondary to trauma[8].

Ubiquitin C-terminal hydrolase-L1 (UCH-L1): UCH-L1 is a protein that mainly resides in the neuronal cell body cytoplasm. It was one of the few biomarker candidates identified based on recent proteomic studies[8].

S100B protein: S100B is an astroglial 11 kDa calcium-binding protein. It is perhaps the most investigated brain injury biomarker to date. Preclinical animal traumatic brain injury (TBI) model data is present. S100B has been studied in TBI of various severities[8].

Glial fibrillary acidic protein (GFAP): GFAP is emerging as the most robust biomarker. GFAP biomarker levels are elevated within 3-34 h in CSF and serum/plasma following severe HIBI and in serum and plasma samples after moderate HIBI[8].

αII-spectrin breakdown products/fragments as cell death markers: more recently, C-terminal BDPs of axonal protein αII-spectrin (SBDP150 and SBDP145) produced by calpain during necrosis, and SBDP120 produced by caspase-3 during apoptosis) have been identified as potential cell death biomarkers in both animal and human CSF samples[8].

Imaging studies

Magnetic resonance imaging (MRI)

The current literature is limited by heterogeneity of MRI timing and patient selection bias. MRI parameters associated with poor outcome include widespread and persistent cortical DWI abnormalities, the combination of cortical and deep gray matter DWI/fluid-attenuated inversion recovery abnormalities, and severe global apparent diffusion coefficient reduction. It can help identify structural abnormalities, such as ischemic areas, bleeding, or swelling. Diffusion-weighted magnetic resonance imaging (DW-MRI)

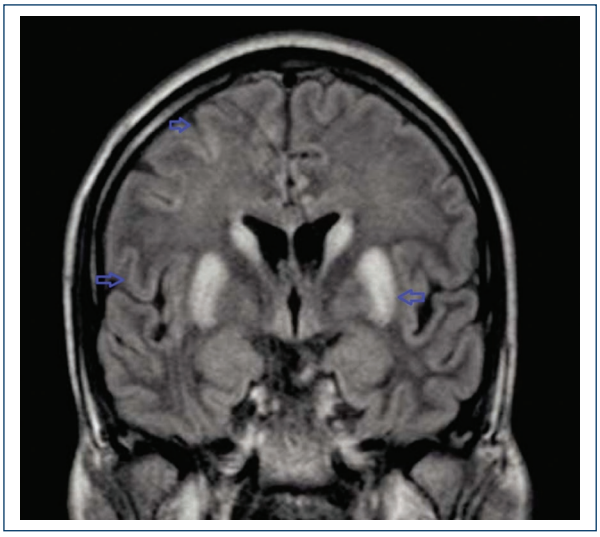


Figure 2. Magnetic resonance imaging coronal section in fluid-attenuated inversion recovery in addition to hyperintensity in basal ganglia and dedifferentiation of gray and white matter, generalized cerebral edema is observed, giving an image of atrophy of the grooves.

is potentially useful for early prediction of neurologic outcome (i.e., before targeted temperature management) in CA patients. The combination of grey matter to white matter ratio on brain computed tomography (CT) and that on DW-MRI, rather than on each modality alone, appears to improve the sensitivity for predicting neurologic outcome after return of spontaneous circulation (ROSC) from CA[3,8-10] (Figs. 3 and 4).

CT scan

After 3-5 days in severe cases, global brain edema may be visualized. Several studies have found that the disappearance of the gray/white junction on non-contrast head CT has been associated with poor outcomes and failure to awaken. A multicenter study showed that reduced gray-white matter ratios predict poor outcome with but with extremely low sensitivity (3.5%-6%), limiting its usefulness in clinical practice. Furthermore, including CT findings in a multivariable model with other prognosticators did not improve the accuracy of prognostication[10].

Treatment/management

The pillar of treatment should be based on prevention, every patient who can potentially be complicated by a CA should have an adequate management of the complication in acute that implies a timely correction of the triggering cause as well as a standardized management of said event by highly qualified personnel.

In the context of neurocritical patient on acute management to reduce the risk of HIBI, several recommendations are suggested.

Taccone et al.[11] suggest the following goals:

Glucose target levels between 80 and 180 mg/dL may be reasonable.

Hemoglobin target to 7-9-g/dL seems reasonable.

Oxygen targeting a SpO_2 between 94% and 97% seems reasonable.

Sodium levels > 135 mEq/L also sodium levels up to 155 mEq/L may be tolerated in such conditions.

Temperature avoids > 38.0°C, due to altered cerebral homeostasis.

Guarantee patient comfort, including control of pain, agitation, anxiety, and shivering.

Arterial blood pressure is the main determinant of CBF. Maintaining a mean arterial pressure (MAP) ≥ 80 mmHg and a cerebral perfusion pressure (CPP) ≥ 60 mmHg, MAP targets can be titrated according to repeated neurological examination.

$PaCO_2$ causes changes in CBF (a 4% change in CBF per mmHg change in $PaCO_2$). If intracranial compliance is reduced, any increase in CBF may increase cerebral blood volume, and thereby intracranial pressure (ICP). On the other hand, excessive hyperventilation can result in cerebral ischemia, and $PaCO_2$ < 35 mmHg should be avoided.

Godoy et al.[12] suggest the following goals:

Maintain temperature goals 36-37°C (core). Hyperthermia can also yield to cerebral hypoxia due to increased metabolism.

Hemoglobin its optimal levels of Hg remain unknown; however, it seems reasonable to reach and maintain Hg values between 7 and 9 g/dL.

Electrolytes and acid basic status balance is the cornerstone. To ensure that Hg dissociation curve remains within functional ranges (p50 = 26-28 mmHg), to reduce the risk of cerebral ischemia and intracranial hypertension pH: 7.35-7.45, temperature between 36 and 37.5°C, to minimize or treat cerebral edema, it is crucial to maintain a slight hyperosmolar state (serum Na+ 140-150 mEq/L) and to avoid hypotonic fluids.

Metabolism, if it is accelerated, O_2 demands increase. Brain metabolism is the main determinant of the rate of cerebral O_2 consumption. Oxygen pressure of the brain parenchyma locally reflects the balance between the supply and consumption of O_2 and should be maintained at values above 18 mmHg. The venous

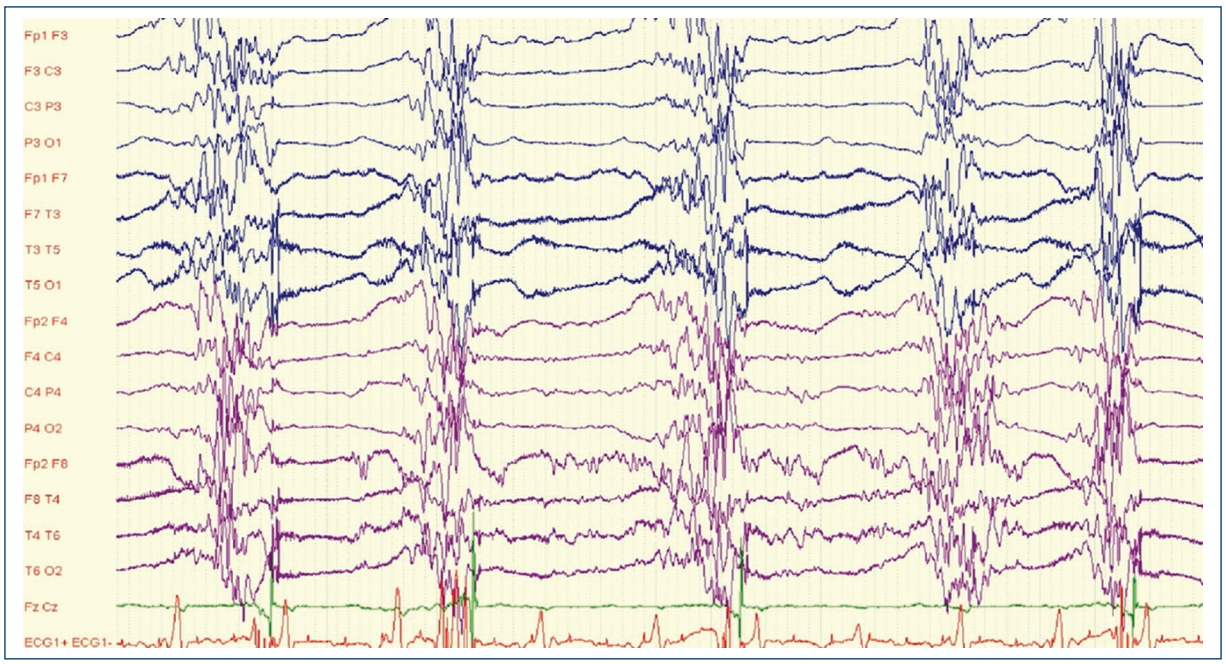


Figure 3. Electroencephalogram of an adult patient after prolonged cardiopulmonary resuscitation, presents a burst-suppression type pattern with a poor prognosis.

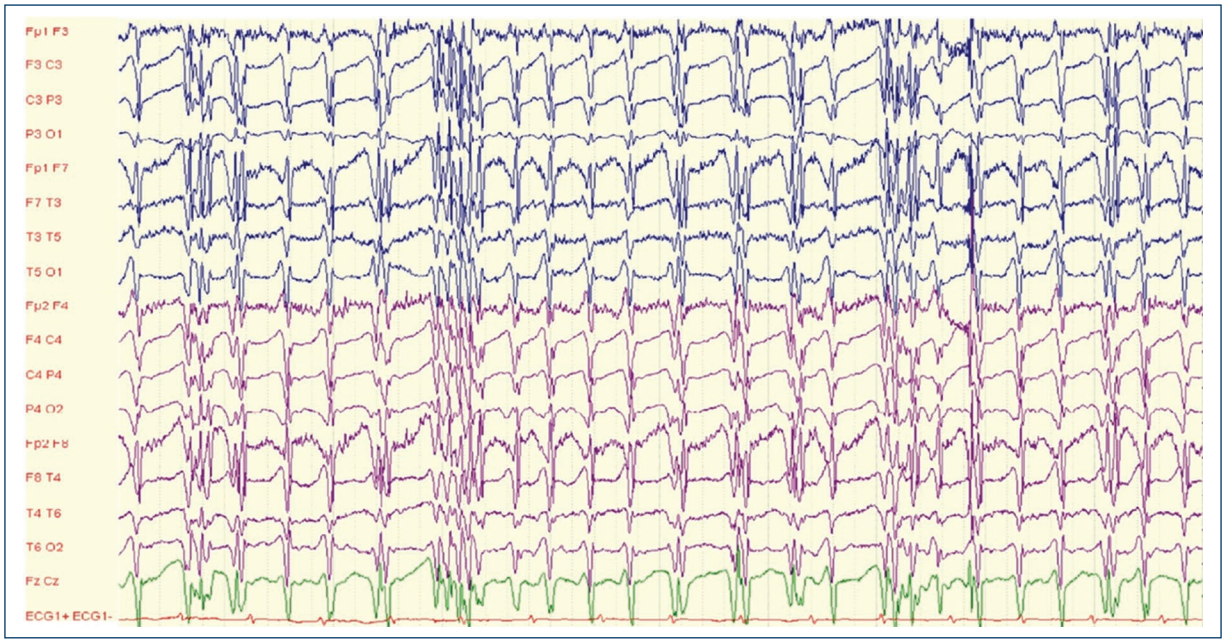


Figure 4. Electroencephalogram showing periodic generalized epileptiform discharges in patient with hypoxic-ischemic brain injury.

oxygen saturation obtained from the jugular bulb ($SvjO_2$), globally represents the O_2 that returns to the general circulation after being consumed by brain cells and should be maintained at values > 55%.

Arterial blood pressure targets include systolic blood pressure > 100-110 mmHg; normal volemia, diuresis > 30 mL/h, preserved peripheral perfusion, and central venous pressure: 6-10 cm H_2O.

Nutrition and glucose control are essential for the damaged brain. Glycemia levels < 110 mg/dL may cause non-ischemic metabolic crises, in contrast, hyperglycemia > 180 mg/dL causes neurotoxic cascades (inflammation, micro thrombosis, edema) and disturbs the homeostasis of the internal environment (hyperosmolarity, dehydration), compromising the immune status, among other alterations.

Target of oxygenation, measures must be taken to achieve PaO_2 80-120 mmHg, and SaO_2 > 95%.

Lung protective ventilation according to available evidence lung-protective ventilation with a controlled mode, tidal volumes between 6 and 8 mL/kg, minimum respiratory rates to ensure levels of $PaCO_2$ between 35 and 45 mmHg, and FiO_2 and PEEP necessary to achieve systemic oxygenation targets as we mentioned above, to prevent mechanical ventilation-induced lung injury (barotrauma, biotrauma, volutrauma) plateau pressure should be kept < 2 cm H_2O, driving pressure < 13 cm H_2O and mechanical power below 17 J/min. It is recommended not to use routinely hyperventilation and to maintain $PaCO_2$ levels between 35 and 45 mmHg.

Detect and treat cerebral edema guaranteeing intracranial pressure goals. The recommended main targets to be achieved should be the following: a) ICP < 22 mmHg; b) CPP: 55-70 mmHg; c) optic nerve sheath diameter (ONSD) < 5.5 mm; d) pulsatility index (PI) < 1.2; and e) Cerebral CT scan without edema signs. Post-CA clinical interventions should include advanced organ support.

Based on promising results from numerous experimental studies from multiple different laboratories, hypothermia has been viewed as an attractive therapy for several acute neurological diseases. Therapeutic hypothermia has been extensively studied at the experimental level and has shown benefit against a variety of mechanisms of brain injury, including reduction in metabolic activity, glutamate release, inflammation, production of reactive oxygen species, and mitochondrial cytochrome c release. In various experimental models of acute brain diseases, several laboratories have consistently demonstrated that hypothermia ameliorates the extent of brain injuries and improves neurologic function. Based on past experimental research, recent clinical studies have established that therapeutic cooling improves neurological outcome from various acute brain insults, including global ischemia after CA, and neonatal hypoxia-ischemia. For other acute cerebral insults, such as ischemic stroke and TBI, the beneficial effect in clinical settings is now under investigation, and its strong neuroprotective effect has been shown consistently by several laboratories in preclinical models[13]. Targeted temperature management and mild hypothermia treatment can improve neurological function, maintain brain cell function, and reduce the risk of stress reactions[13,14]. In humans, hypothermia has been found to be neuroprotective with a significant impact on mortality and long-term functional outcome only in CA and neonatal hypoxic-ischemic encephalopathy. Clinical trials have explored the potential role of maintaining normothermia and treating fever in critically ill brain-injured patients, physiologic interactions of thermoregulation, effects of thermal modulation in critically ill patients, proposed mechanisms of action of temperature modulation, and practical aspects of targeted temperature management[15].

Rehabilitation and support

A strong consensus was found in favor of assessments being conducted by appropriately trained staff. Patients with difficulties in performance of daily activities should be assessed by a clinician trained in the use of whichever scales are chosen to < ensure consistency of their use within the team and an understanding of their purposes and limitations[16].

There was consensus between the Dutch, UK, and US guidelines that patients should be assessed to enable progress to be monitored throughout recovery and multiple measures to allow for changes in setting, goals, and ability levels. The US guidelines recommend multiple activities with the primary assessing function and secondary including measures of impairment, activity limitation, and quality of life. The Scottish Intercollegiate Guidelines Network recommended using a range of assessment tools to assist goal-setting[17].

Neuroplasticity is involved in the normal processes of learning, memory, and skill acquisition. This same capacity of brain reorganization with experience supports neural repair after brain damage. Endogenous neuroplasticity in recovery likely has a more sensitive and critical time period to intervention beginning in the late acute and subacute periods of recovery after brain damage, such as TBI or stroke. This suggests that patients are most likely to benefit from rehabilitative interventions that promote neuroplasticity in the early days and weeks after brain injury. A goal of recent investigations has been to find strategies and treatments that may extend and enhance endogenous neuroplasticity. Nevertheless, neuroplasticity can play a role later, even in chronic periods of recovery, with skill learning and improvement in performance. Strategies to restore function

and improve compensations have been demonstrated during chronic periods after brain injury. The process of neuroplasticity and brain reorganization with experience, learning, and practice is a lifelong capacity that contributes to learning in an undamaged nervous system, as well as recovery after developing neurological dysfunction[17].

Considerations on obstetric patients

We found no differences in this review in the approach to obstetric patients[18,19].

Conclusion

HIBI is the drastic and irreversible result of neurological injury, almost always occurring as a consequence of CA or in patients receiving suboptimal neurocritical care. The diagnosis of this clinical entity is based on a detailed neurological evaluation that includes clinical tests, as well as special studies that include neuroimaging, neurophysiology, metabolic, and biomarker studies. The most important treatment is based on prevention, every health unit must have a rapid response team for brain code, CA code, as well as intensive care units with a team trained to perform timely care and interventions in critical patients, with special emphasis on neurocritical care to prevent or limit the severity of a condition that potentially causes neurological damage. Rehabilitation options for HIBI must involve a multidisciplinary approach, including medical management, physical and occupational therapy, speech therapy, and psychological support for both the patient and their family.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Di Muzio B, Majeed A, Kemp W, Abdeldjalil B, Yu Jin T, Gerstenmaier J, et al. Hypoxic-ischemic encephalopathy (adults and children); 2022. Available from: https://radiopaedia.org/articles/hypoxic-ischemic-encephalopathy-adults-and-children-1?lang=us
2. Messina Z, Hays Shapshak A, Mills R. Anoxic Encephalopathy. Treasure Island, FL: StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/nbk539833
3. Heinz UE, Rollnik JD. Outcome and prognosis of hypoxic brain damage patients undergoing neurological early rehabilitation. BMC Res Notes. 2015;8:243.
4. Mason Sharma A, Birnhak A, Sanborn E, Bhana N, Kazmi K, Thon J, et al. Neuroimaging mimics of anoxic brain injury: a review. J Neuroimaging. 2023;33:467-76.
5. Burridge J, Alt Murphy M, Buurke J, Feys P, Keller T, Klamroth-Marganska V, et al. A systematic review of international clinical guidelines for rehabilitation of people with neurological conditions: what recommendations are made for upper limb assessment. Front Neurol. 2019;10:567.
6. Gutte S, Azim A, Patnaik R. Biomarkers in hypoxic brain injury: methods, discoveries, and applications. In: Rajendram R, Preedy VR, Patel VB, editors. Biomarkers in trauma, injury and critical care. Biomarkers in disease: methods, discoveries and applications. Cham: Springer; 2022.
7. Rayi A, Mandalaneni K. Encephalopathic EEG patterns. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/nbk564371 [Last accessed on 2023 Mar 04].
8. Fugate JE. Anoxic-ischemic brain injury. Neurol Clin. 2017;35:601-11.
9. Wang KK, Yang Z, Zhu T, Shi Y, Rubenstein R, Tyndall JA, et al. An update on diagnostic and prognostic biomarkers for traumatic brain injury. Expert Rev Mol Diagn. 2018;18:165-80.
10. Keijzer HM, Hoedemaekers CW, Meijer FJ, Tonino BA, Klijn CJ, Hofmeijer J. Brain imaging in comatose survivors of cardiac arrest: pathophysiological correlates and prognostic properties. Resuscitation. 2018; 133:124-36.
11. Taccone FS, De Oliveira Manoel AL, Robba C, Vincent JL. Use a "GHOST-CAP" in acute brain injury. Crit Care. 2020;24:89.
12. Godoy DA, Murillo-Cabezas F, Suarez JI, Badenes R, Pelosi P, Robba C. "THE MANTLE" bundle for minimizing cerebral hypoxia in severe traumatic brain injury. Crit Care. 2023;27:13.
13. Kurisu K, Kim JY, You J, Yenari MA. Therapeutic hypothermia and neuroprotection in acute neurological disease. Curr Med Chem. 2019;26:5430-55.
14. Wang Y, Huang C, Tian R, Yang X. Target temperature management and therapeutic hypothermia in sever neuroprotection for traumatic brain injury: clinic value and effect on oxidative stress. Medicine (Baltimore). 2023;102:e32921.
15. Rincon F. Targeted temperature management in brain injured patients. Neurosurg Clin N Am. 2018;29:231-53.
16. Katz DI, Dwyer B. Clinical neurorehabilitation: using principles of neurological diagnosis, prognosis, and neuroplasticity in assessment and treatment planning. Semin Neurol. 2021;41:111-23.
17. Di Filippo S, Godoy DA, Manca M, Paolessi C, Bilotta F, Meseguer A, et al. Ten rules for the management of moderate and severe traumatic brain injury during pregnancy: an expert viewpoint. Front Neurol. 2022;13:911460.
18. Kho GS, Abdullah JM. Management of severe traumatic brain injury in pregnancy: a body with two lives. Malays J Med Sci. 2018;25:151-7.
19. Schaap TP, Overtoom E, van den Akker T, Zwart JJ, van Roosmalen J, Bloemenkamp KW. Maternal cardiac arrest in the Netherlands: a nationwide surveillance study. Eur J Obstet Gynecol Reprod Biol. 2019;237:145-50.

Revista Médica del
Hospital General de México

PERMANYER

Check for updates

REVIEW ARTICLE

Is humanity undergoing a transition to reproductive specialization? Insights on the evolution of modern societies to superorganisms

Edwin F. Herrera-Paz

COCINH-LAB Honduras, Gobierno de la República de Honduras, Tegucigalpa MDC; Faculty of Medicine, Universidad Católica de Honduras, Campus San Pedro y San Pablo, San Pedro Sula. Honduras

Abstract

A current discussion centers on whether human societies are undergoing a major evolutionary transition in individuality (METI) toward superorganisms. A METI typically involves a population composed of independent units evolving to form a new unit of a higher level of complexity, as for instance, the emergence of multicellular organisms from unicellular organisms, or the evolution of superorganisms, such as beehives. It has been proposed that for a METI to occur, certain key criteria must be met, including division of labor, exponential increase in size, inseparability, and reproductive specialization. All of these characteristics have been documented in human populations over the past 12,000 years, except for reproductive specialization. This involves that only a fraction of the population carries out reproductive functions, while the rest performs maintenance tasks. Recently, human populations are experiencing the so-called "demographic transition," characterized by a decrease in infant mortality, followed by a decrease in birth rates. The causes of this transition are mainly sociocultural, leading to diminished reproductive competition, which, in turn, could lead to biological infertility. This begins a positive feedback loop of declining fertility, potentially leading to a demographic winter and the risk of extinction of modern societies. To prevent such an outcome, governments will probably implement rescue measures that could lead to reproductive specialization. The study of transitions has medical importance because they may cause shifts in health-disease landscapes.

Keywords: *Complexity. Evolution. Extinction. Infertility. Reproduction. Transitions.*

Introduction

In recent years, abundant literature has emerged analyzing the evolution of life toward progressively more complex forms. In addition, it has been assessed that most of the characteristics present in biological evolution are also present in the sociocultural evolution of human populations[1]. It is known that biological complexity does not always evolve in a linear, monotonic manner, but sometimes increase in leaps toward higher hierarchical levels. Such leaps have been termed "major evolutionary transitions in individuality," or (METI)[2].

During the evolutionary period of time that comprises METI, highly independent, autonomous, free-living individuals, lose most of their independence to become part of a new whole. Evolutionary transitions within biological evolution can be divided into two categories: (1) an egalitarian transition implies that two organisms of different species come together in symbiosis or endosymbiosis to form a more complex unit. The classical example is the emergence of eukaryotic cells from an endosymbiotic process between two species of prokaryotes. (2) a fraternal transition occurs when

Correspondence:
Edwin F. Herrera-Paz
E-mail: eherrera@unicah.edu

Date of reception: 06-01-2024
Date of acceptance: 28-05-2024
DOI: 10.24875/HGMX.24000001

Available online: 21-11-2024
Rev Med Hosp Gen Mex. 2025;88(2):88-95
www.hospitalgeneral.mx

individuals of the same kind progressively become more cohesive and interdependent, such that the population gradually transforms into an individual of a higher hierarchical level. The two main examples of fraternal transitions are the emergence of multicellular organisms and the origin of superorganisms (complex colonies) in some eusocial species of ants and bees.

Recent efforts to operationalize the parameters involved in METIs have resulted in the identification of at least four common features: (1) increasing interdependence between individuals, resulting in inseparability from the group; (2) labor specialization or division of labor; (3) a drastic increase in size, and (4) reproductive specialization, i.e., reproductive function is limited to a few individuals in the community such as germ cells and stem cells in multicellular organisms, or queens and drones in a beehive[3,4]. Additional factors involved in the evolution toward greater complexity are progressive enhancements in communications systems, such as the evolution of endocrine and paracrine signaling systems in multicellular organisms, or complex chemical signaling in ants-and the emergence of more abundant and efficient energy sources[5].

It has been noted that the sociocultural and technological evolution of human beings in the past 12,000 years exhibits most of the characteristics of a METI. Therefore, it has been suggested that human societies may be experiencing a fraternal METI toward human superorganisms[3,6].However, unlike previous METIs, the evolution of human superorganisms would be triggered by sociocultural and technological factors, rather than exclusively by biological ones.

The sole remaining factor to affirm that human societies are evolving into superorganisms is reproductive specialization, which in multicellular organisms and superorganisms is evidenced by a strong reproductive skew among group members[6]. Moreover, humans exhibit less reproductive skew than other mammalian species[7]. However, the possibility that human societies may be experiencing the beginning of a transition toward reproductive specialization has not been examined so far. Thus, finding signals that indicate that humanity is experiencing such a transition is important for assessing a METI driven by sociocultural and technological factors. This may have profound implications for future healthcare, medicine, and epidemiology. As an example from the recent past demographic and economic transitions have changed health-disease landscapes worldwide, increasing the incidence of cardiovascular and metabolic diseases[8]. As I will argue, the decay in fertility rates in modern human societies may be an early sign of a transition to reproductive specialization. This paper is not intended to be an exhaustive review of the causes of human infertility, but rather to assess the likelihood of reproductive specialization emerging within economically and technologically advanced human societies in the coming decades, in the larger framework of a human METI.

Reproductive specialization in multicellular organisms and superorganisms

I will examine reproductive specialization in multicellular organisms, specifically humans, at two levels of biological complexity: cellular reproduction (division) and the reproduction of entire multicellular organisms. At the most basic level, cells must divide to (1) give rise to an adult multicellular individual with a multiplicity of cellular specializations, and (2) to replace old, specialized cells that are continually dying. Most multicellular organisms begin their lives as a totipotent unicellular organism, the zygote, which passes this totipotency to the first generations. From a technical point of view, these first generations are pluripotent, capable of generating cells belonging to the three embryonic germ layers. During human embryogenesis, cells, induced by epigenetic modifications, progressively lose this capacity. Throughout the rest of a human's life, tissues regenerate from a pool of multipotent stem cells (MSC) that continue to divide. These MSCs are capable of generating all types of specialized cells, but each type is restricted to a specific organ or system[9,10].

MSCs from different tissues and their committed direct descendants have a high reproductive capacity and are responsible for maintaining the cell population in the organ. Unlike these, specialized cells have a limited reproductive capacity. The path from totipotency to specialization is mostly irreversible *in vivo*, although the reprogramming of specialized cells to pluripotent cells *in vitro* is possible by inducing the expression of Yamanaka transcription factors, a procedure with enormous therapeutic potential[11]. The natural pathway leading from multipotentiality to a specialized cell is determined by signals from the extracellular matrix, as well as by intercellular and mitochondrial signaling[12-14]. These signals induce epigenetic changes, the most important of which is gene silencing through DNA methylation and histone modification[15,16]. In the process of cellular replacement during the lifetime of an individual, reproductive specialization entails that the task of

generating new specialized cells is limited to MSCs in each organ.

At the next level of biological complexity, a multicellular organism with sexual reproduction reproduces by generating new multicellular individuals. Here, the task of generating new individuals falls exclusively on the gametes, for which there is, during early embryogenesis, an early sequestration of an immortal germline: the germplasm[17]. Similarly, once the gametes give rise to a zygote and therefore to a new organism, their somatic descendants lose that capacity. Reproductive specialization means that only cells of the germline are responsible for the generation of new multicellular individuals.

Finally, at the highest level of biological complexity, in some eusocial species of bees and ants, the tasks of generating new individuals for the colony and establishing new colonies are handled by a few individuals, such as queens and drones in honeybees. In these species, the workers play the role of the "somatic line", while the reproductive individuals assume the role of a "germline"[18]. The mechanisms that give rise to reproductive specialization and sexual dimorphism vary widely among different species of eusocial insects and range from phenotypic plasticity influenced by the environment (epigenetic determination) to being fully determined by the genotype[19,20], which is evidence of convergent evolutionary pathways, and though, of an underlying biological advantage offered by these traits.

Biological advantages of reproductive specialization

In both sexually reproducing organisms and superorganisms, non-reproductive individuals specialize in tasks that contribute to the maintenance and survival of the group, i.e., somatic specialized cells in the multicellular organism or workers in honeycombs. Their main role is to be an interface with the environment to ensure the survival of the germplasm. Since there is no reproductive competition among these non-reproductive individuals, the characteristics of each sex are not necessary for them. For instance, in eusocial insects, the workers are usually asexual, unlike drones and queens, which exhibit notable differences between them, i.e. sexual dimorphism. The loss of sexual characteristics in non-reproductive individuals represents a form of evolutionary phenotypic simplification (simplification of individuals coupled to an increase in group complexity as an evolutionary mechanism can be reviewed in references[3,21,22]).

An accepted explanation for the evolution of reproductive specialization is that to avoid subversion within the group, individuals must be genetically similar, and this similarity is achieved through a genetic bottleneck, marking a new beginning for each organism or superorganism. Genetic homogeneity is attained because all cells descend from a single cell (the zygote) in the case of organisms, or from a single queen, in the case of eusocial insects. However, an alternative (or perhaps complementary) explanation for the evolution of reproductive specialization is the division of labor, which results in the maximization of energetic efficiency for the group. That is, cooperative communities where individuals specialize in a specific task, including reproduction, are economically more efficient than those in which "everyone does everything," providing the group with a competitive advantage. Therefore, reproductive specialization could be part of a broader division of labor. Division of labor and other features seen in the transition from complex populations to organisms and superorganisms, primarily evolve as traits related to the survival of the group rather than the survival of the individual (for a review on multilevel selection see reference[23]). Reproductive specialization allows the energy of a few individuals to be focused on the task of reproduction.

Sexual dimorphism in humans

Sexual dimorphism can be defined as the physical or behavioral characteristics that differentiate males from females of the same species[24]. I will extend the usual definition to include all the differences present at various levels of biological complexity between both sexes. Table 1 shows the most prominent dimorphic features at the different levels.

At a molecular level, men are differentiated from women by the presence of a Y chromosome, and specifically, by the presence of the SRY gene. The expression of this small gene –which encodes a transcription factor– at the 6th week of gestation in the bipotent gonad, determines sex through the activation of a gene cascade that leads to the formation of testes[25]. In women, the absence of the SRY gene determines a different activation pathway lead by WNT-4. In addition to SRY, the Y chromosome harbors important genes for spermiogenesis.

Once the testis is differentiated, Leydig cells actively secrete testosterone. In general terms, testosterone and its derivative hormone, dihydrotestosterone, establish the virilization of the external genitalia, giving rise to the penis and scrotum. In the absence of testosterone, the genitals develop into vulvar structures and the

Table 1. Sexual dimorphism in humans at different levels of biological complexity. Unfolding of the male and female phenotypes and successful procreation requires integrity in the sequential activation of complex genetic networks

Level of biological complexity	Males	Females
Molecular	Presence of a Y chromosome	Absence of a Y chromosome
	Presence of a SRY gene	Absence of a SRY Gene
Gondal	Presence of testis, testosterone secretion	Presence of ovary, estradiol, and progesterone secretion
Genital	Presence of the scrotum and penis, the development of Wolf conducts derivatives	External genitalia: Vulvar structures, clitoris, lower 2/3 of vagina. Internal genitalia: Uterus and fallopian tubes
Secondary sexual characteristics	Larger lean mass, stronger complexion, presence of facial hair, android distribution of pubic hair	Larger cosmetic adipose tissue in breasts and hips, gynecoid distribution of pubic hair
Sexual identity	Male brain	Female brain
Sexual orientation	Attracted by females	Attracted by males

lower two-thirds of the vagina. Similarly, the secretion of testosterone in the fetus and the early post-partum period produces cerebral virilization, probably being the main determinant of male sexual identity and orientation[26]. In addition, the Sertoli cells of the embryonic testicle secrete the anti-Müllerian hormone, which prevents the formation of fallopian tubes and the uterus. Testosterone secretion is interrupted during childhood but resumes in adolescence with the secretion of pituitary gonadotropic hormones, leading to the development of male secondary sexual characteristics. In the absence of testosterone, female secondary sexual characteristics, conditioned by estrogens and progesterone, predominate (a comprehensive review of human sexual development can be found in Rey et al.[27]).

Evolutionarily speaking, sexual dimorphism at all levels –from the presence or absence of a sexual chromosome to the generation of testes or ovaries, the emergence of secondary sexual characteristics, and behavior that leads to the search for a sexual partner and subsequently to successful sexual intercourse and pregnancy– aims to increase the fertility of the individual. They constitute fine clockwork mechanisms with multiple activation cascades that involve many genes. Disruption of these genes can lead to disorders of sex development, conditions associated with reproductive development, intersex, and variations in sex characteristics, all of which may have a negative impact on fertility.

The evolutionary mechanisms of sexual dimorphism arise from a type of selection different from natural selection, coined by Charles Darwin as "sexual selection." Traits related to sexual selection do not contribute to the survival of the individual, but only to its ability to reproduce. For these traits to emerge and be maintained in populations, strong reproductive competition between individuals of the same sex is required[28]. Consequently, the loss of reproductive competition could lead to a process of progressive simplification of sexual dimorphism and a drop in fertility rates.

Demographic transition triggers sociocultural infertility

In the past two centuries, humanity has experienced enormous advances in public health and therapeutics, which, along with alimentary transitions, have resulted in a drastic drop in infant mortality rates. The decline in mortality rates has been followed by a decline in fertility rates. The changes in the demographic composition of countries due to these two phenomena have been coined "the demographic transition"[29]. Typically, pre-transition population pyramids, as their name indicates, are triangle-shaped, with a wide base that represents a growing population with high natality rates and high mortality across all age groups. During the demographic transition, as both birth and death rates decrease, the base of the pyramid becomes narrower and this narrowness ascends, gradually reversing the shape of the pyramid, with a large aging population in the upper segments, and a narrow base that represents the youngest segment (an example of population pyramids from some Latin-American countries can be found in reference 8).

The demographic transition began in Europe in the 18th century and gradually spread to the rest of the world. During recent decades, the fertility rate in high-income and some middle-income countries has fallen below the population replacement rate of 2.1 children per woman, which is a component of the so-called "second demographic transition"[30].

The sociocultural causes of demographic transitions are varied, all resulting in a psychosocial shift toward a decline in reproductive drive. Most probably, the main triggering factor of the current decline in birth rates in modern societies is the economic transition, i.e., when society changes from a state of deprivation to an abundance of food and other resources. As a society prospers and therefore the basic needs of its inhabitants are met, the energy consumption per capita increases, which in turn raises the costs of childrearing; consequently, there is a tradeoff from quantity to quality in procreation[31]. In addition, sociocultural changes in gender equality have allowed women to obtain better education and enter the workforce. As a result, women's productive activity competes with the procreative function, such that parenthood is postponed and the number of children per woman decreases. Thus, in modern advanced human societies a tradeoff between reproduction and production occurs[30]. Finally, the decline in reproductive activity in humans and other species could be influenced by endocrine and behavioral changes induced by increased population density[32,33]. In addition, sociocultural changes could barely reduce fertility rates without technological advances in contraceptive methods.

For practical purposes, I will divide the decline in fertility among modern human groups into two types: (1) sociocultural infertility, which is voluntary and motivated by the sociocultural factors listed above, and (2) environmental/biological infertility, determined by those factors that decrease the probability of pregnancy despite the attempts to achieve it. Table 2 summarizes the main causes of the declining fertility rates and their possible impact in fertility parameters. Most likely, the increase in sociocultural infertility in modern human populations predates the increase in environmental/biological infertility. Sociocultural infertility and reduction in child mortality rates may lead to a progressive increase in environmental/biological infertility due to loss of reproductive competition[22,34]. Under a regime of poor reproductive competition due to sociocultural factors, fertile individuals have the same probability of reproducing as less fertile ones, not only because many of the biologically fertile individuals voluntarily postpone or avoid parenting, but also because the less fertile are now able to reproduce due to improvements in assisted reproduction technologies.

Table 2. Possible causes and outcomes of fertility decline in post-transition societies

Causes of sociocultural/technological infertility
Raise in coasts of childrearing
Better education and work opportunities for women
Effective contraceptive methods
Causes of biological/environmental infertility
Loss of reproductive competition
Endocrine disruptors
Psychological response to stress and population density
Possible negative outcomes in fertility
Drop in testosterone levels in men
Drop in sperm counts
Raise in the prevalence of Polycystic Ovary Syndrome
Raise in the proportion of non-heterosexual individuals
Loss of sexual dimorphism

What might be the biological repercussions of the loss of long-term reproductive competition? First, mutations that decrease sexual dimorphism and fertility can easily survive and increase in frequency in the population through individuals with low fertility who reproduce using assisted reproduction technologies. Consequently, there will be a loss of negative (purifying) selection on genes that maintain sexual dimorphism and fertility. Second, there may be a loss of positive (directional) selection, obliterating adaptation to environmental insults to fertility. The most outstanding example of environmental noxa detrimental to fertility is endocrine disruptors[35].

Evidence of increasing biological/ environmental infertility

A progressive decline in the biological fertility of human populations is evidenced by several parameters linked to fertility. In men, a gradual decline in mean sperm counts has been observed[36], as well as in mean testosterone levels[37]. In Western women, consultations for polycystic ovary syndrome have increased in recent years[38].

On the other hand, there is a growing social acceptance of individuals who self-identify as non-binary or do not conform to the traditional classification of two genders, with the emergence of the so-called "gender ideology"[39]. Although the genesis of variations in traditional sexual partner-seeking behavior is largely presumed to be cultural, the underlying influence of

biological/environmental factors cannot be ignored. In this context, a genome-wide association study found that the effect of multiple genetic variants accounted for between 8% and 25% of the variation in homosexual behavior[40]. A possible decline in the proportion of heterosexual couples may be a contributing factor to decreasing birth rates.

The integrity of endocrine function is vital for finding a sexual partner and for procreation, and even small variations in hormonal levels can produce large systemic effects. Endocrine disruptors are natural or synthetic chemical substances that interfere with physiological endocrine systems either by blocking or mimicking hormones, with multiple consequences for human health. They can enter the body through different routes, such as inhalation, ingestion, or direct contact. Among the most abundant are plastics, such as bisphenol A and phthalates; some herbicides such as atrazine; and products widely used in manufacturing such as dioxins, perchlorates, polychlorinated biphenyls, polybrominated diphenyl ethers, and per/polyfluoroalkyls. Most endocrine disruptors have a negative impact on fertility[35,41]. The increasing environmental accumulation of these substances could be responsible, at least in part, for the decreased biological fertility and variations in sexual behavior.

What should be the effect of increased exposure to endocrine disruptors in a population with a high reproduction drive? Although an initial drop in natality rates would be observed, positive selection for individuals harboring genetic variants that confer resistance to endocrine disruptors would rapidly occur. In this scenario of high reproductive competition, the population would become resistant in a few generations, without any further impact of the substances on fertility rates. Conversely, in a population with a low reproductive drive such as modern advanced human societies, the evolution of resistance to endocrine disruptors that are harmful for fertility should not be expected. A low reproductive drive results in low reproductive competition. Therefore, over time, biological parameters of fertility, as well as sexual dimorphism at all levels, should decrease. This, in turn, would lead to further drops in fertility, lower reproductive competition, further increments of infertility, and so on, in a positive feedback loop that could potentially lead to the extinction of humankind.

Possible future paths to human reproductive specialization

If the presence of environmental endocrine disruptors continues to grow, and the lack of reproductive competition due to sociocultural infertility leads to an accumulation of deleterious mutations in fertility genes (sexual simplification), then the progressive decrease in birth rates worldwide must be an asymmetric, largely irreversible phenomenon. Therefore, a rebound of fertility in modern societies to past levels is unlikely. The consequence is an aging population, which would radically change the demographic, economic, and epidemiological landscapes of countries in the coming decades[42,43].

The evolution toward reproductive specialization must include two components: (1) decreased fertility in the majority of individuals and (2) increased fertility in the remaining individuals, sufficient for population replacement. Together, these two components would raise the reproductive skew. Although the former is now occurring in modern societies, there is still no evidence of the latter. Given the apparent inevitability of an aging population, in an effort to increase fertility rates, governments of countries that are in advanced stages of the demographic transition (like some countries from the European Union) usually offer economic incentives to boost fertility[44].

One scenario (although highly speculative) that could lead to sexual specialization is that, in an attempt to avoid demographic winter and its negative economic impact, governments could significantly increase monetary incentives for fertility. Then, a fertile fraction of the population might take advantage of these high economic revenues for reproduction, turning the task of procreation into an economic activity. To reverse depopulation, this fertile fraction must raise fertility rates needed for population replacement. However, if biological/environmental infertility continues to increase, this approach would not be feasible in the long run, and the reproductive fraction would need support from advanced assisted reproduction technologies.

If birth rates continue to drop and economic incentives fail to restore fertility rates, an extreme scenario could arise in which, facing an imminent extinction of human societies, governments might take complete control of the task of reproduction. This could be feasible, as ectogenesis technologies improve[45]. Although this may seem a reminiscence of the dystopic novel by Aldous Huxley “Brave New World”, the decimation of the most advanced human societies due to lack of reproduction is a real possibility[34], which may eventually require extreme measures. Both of the above scenarios could lead to reproductive specialization, with a fraction of the population (individuals or governments) assuming the task of reproduction (Fig. 1).

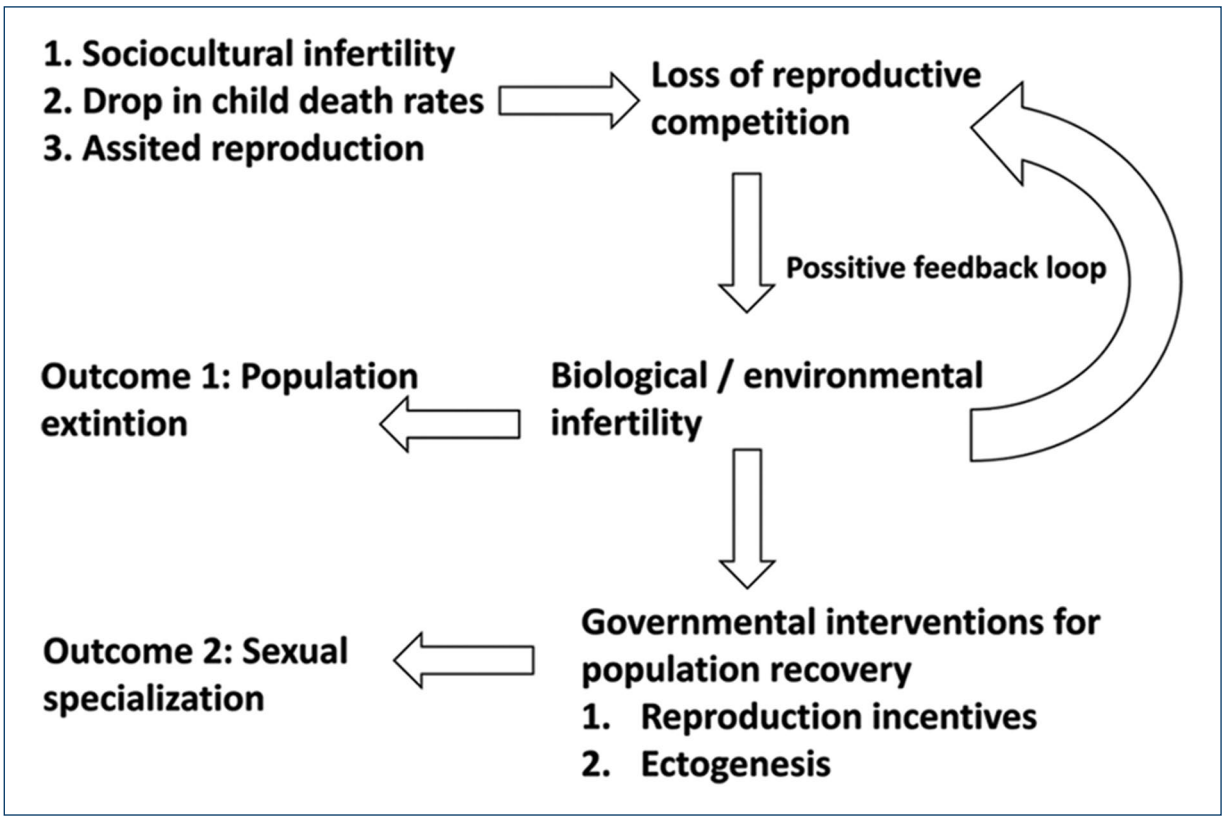


Figure 1. Possible outcomes of raising infertility in human populations. Loss of reproductive competition derives in a raise of biological/environmental infertility, further lowering reproductive competition in a positive feedback loop. Measures imposed by governments could derive in sexual specialization.

Conclusion

Currently, superorganisms (organisms composed of organisms) such as the beehive or the anthill, constitute the most advanced level of biological complexity on Earth. Whether or not human societies are completing a transition to human superorganisms guided by an interaction of sociocultural, technological, and biological factors is controversial, and one of the reasons is the absence of sexual specialization. However, recent economic and demographic transitions have been the genesis of an increasing decline in fertility rates in modern societies, due to a positive feedback cycle that could lead to sexual simplification and increased biological infertility. The potential rescue measures implemented by governments in response to the imminent demographic winter could limit the task of reproduction to a fraction of the population, or even to governments themselves, leading to reproductive specialization. As a byproduct, reproductive specialization may increase genetic homogeneity, a common characteristic of organisms and superorganisms. The emergence of a strong reproductive skew in advanced human societies in the upcoming decades would be an unequivocal sign that we are in an ongoing METI toward human superorganisms. Finally, the impact of reproductive transitions on future human psychology, social interactions, political systems, and healthcare systems (among others) is uncertain. Governments, institutions, and the public must be aware that modern societies are thriving in an era of rapid changes which require high flexibility and adaptability.

Acknowledgments

The author would like to thank Dr. Y. Carmel, at Technion Israel Institute of Technology, and the participants to the Batsheba De Rothschild seminar “Socio-Technological Evolution of the Human Species: is Humanity undergoing an evolutionary transition?” (https://ste2019.net.technion.ac.il/program/) held at Safed, Israel, 2019, for enlightening talks on evolutionary transitions in individuality. I am also grateful to Dr. H. M. Ramos-Zaldivar for reviewing the manuscript and suggesting important changes.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The author declares that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The author declares that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Portin P. A comparison of biological and cultural evolution. J Genet. 2015;94:155-68.
2. Hanschen ER, Davison DR, Grochau-Wright ZI, Michod RE. Individuality and the major evolutionary transitions. In: Gissis SB, Lamm E, Shavit A, editors. Landscapes of Collectivity in the Life Sciences. Cambridge: MIT Press; 2018. p. 255-68.
3. Herrera-Paz EF. Evolution to Complexity: From Unanimated Matter to the Universal Superorganism. Charleston: Createspace; 2014.
4. Carmel Y, Shavit A. Operationalizing evolutionary transitions in individuality. Proc Biol Sci. 2020;287:20192805.
5. Herrera-Paz EF. A universal trend: non-living, biological, and sociocultural/technological transitions in evolution towards complexity. 2022. Available from: https://www.researchgate.net/publication/359367257_Title_A_universal_trend_Non-living_biological_and_socioculturaltechnological_transitions_in_evolution_towards_complexity
6. Carmel Y. Human societal development: is it an evolutionary transition in individuality? Philos Trans R Soc Lond B Biol Sci. 2023;378:20210409.
7. Ross CT, Hooper PL, Smith JE, Jaeggi AV, Smith EA, Gavrilets S, et al. Reproductive inequality in humans and other mammals. Proc Natl Acad Sci U S A. 2023;120:e2220124120.
8. Herrera-Paz EF. Biodemography research and the history of Central American and Northwestern South American Populations. In: Biological Anthropology of Latin America. Washington, D.C.: Smithsonian Press; 2019. p. 127-47.
9. Yilmaz A, Benvenisty N. Defining human pluripotency. Cell Stem Cell. 2019;25:9-22.
10. Worku MG. Pluripotent and multipotent stem cells and current therapeutic applications: review. Stem Cells Cloning. 2021;14:3-7.
11. Aguirre M, Escobar M, Forero Amézquita S, Cubillos D, Rincón C, Vanegas P, et al. Application of the Yamanaka transcription factors Oct4, Sox2, Klf4, and c-Myc from the laboratory to the clinic. Genes (Basel). 2023;14:1697.
12. Walma DA, Yamada KM. The extracellular matrix in development. Development. 2020;147:dev175596.
13. Rowton M, Guzzetta A, Rydeen AB, Moskowitz IP. Control of cardiomyocyte differentiation timing by intercellular signaling pathways. Semin Cell Dev Biol. 2021;118:94-106.
14. Chakrabarty RP, Chandel NS. Mitochondria as signaling organelles control mammalian stem cell fate. Cell Stem Cell. 2021;28:394-408.
15. Greenberg MV, Bourc'his D. The diverse roles of DNA methylation in mammalian development and disease. Nat Rev Mol Cell Biol. 2019;20:590-607.
16. Elsherbiny A, Dobreva G. Epigenetic memory of cell fate commitment. Curr Opin Cell Biol. 2021;69:80-7.
17. Aanen DK. Germline evolution: sequestered cells or immortal strands? Curr Biol. 2019;29:R799-801.
18. Lehtonen J, Helanterä H. Superorganismal anisogamy: queen-male dimorphism in eusocial insects. Proc Biol Sci. 2020;287:20200635.
19. Taylor BA, Reuter M, Sumner S. Patterns of reproductive differentiation and reproductive plasticity in the major evolutionary transition to superorganismality. Curr Opin Insect Sci. 2019;34:40-7.
20. Sieber KR, Dorman T, Newell N, Yan H. (Epi) genetic mechanisms underlying the evolutionary success of eusocial insects. Insects. 2021;12:498.
21. McShea DW, Brandon RN. Biology's First Law: The Tendency for Diversity and Complexity to Increase in Evolutionary Systems. Chicago: University of Chicago Press, 2010.
22. Herrera-Paz EF. Simplification as a Mechanism that Drives Evolution to Biological and Sociocultural Complexity; 2021. Available from: https://www.researchgate.net/publication/354742297
23. Jeler C. Explanatory goals and explanatory means in multilevel selection theory. Hist Philos Life Sci. 2020;42:36.
24. Mori E, Mazza G, Lovari S. Sexual dimorphism. In: Vonk J, Shackelford T, editors. Encyclopedia of Animal Cognition and Behavior. Cham: Springer International Publishing; 2022. p. 6389-95.
25. Berta P, Hawkins JB, Sinclair AH, Taylor A, Griffiths BL, Goodfellow PN, et al. Genetic evidence equating SRY and the testis-determining factor. Nature. 1990;348:448-50.
26. Hines M, Constantinescu M, Spencer D. Early androgen exposure and human gender development. Biol Sex Differ. 2015;6:1-10.
27. Rey R, Josso N, Racine C. Sexual differentiation. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext. South Dartmouth: MDText.com, Inc.; 2020.
28. Clutton-Brock T. Reproductive competition and sexual selection. Philos Trans R Soc Lond B Biol Sci. 2017;372:20160310.
29. Cosio-Zavala ME. The demographic transition. In: Charbit Y, editor. Demographic Dynamics and Development. Hoboken: John Wiley and Sons; 2022. p. 1-26.
30. Lesthaeghe R. The second demographic transition, 1986–2020: sub-replacement fertility and rising cohabitation-a global update. Genus. 2020;76:1-38.
31. Fernihough A. Human capital and the quantity-quality trade-off during the demographic transition. J Econ Growth. 2017;22:35-65.
32. Ramsden E, Adams J. Escaping the laboratory: The rodent experiments of John B. Calhoun and their cultural influence. J Soc Hist. 2009;42:761-92.
33. Suvorov A. Population numbers and reproductive health. Endocrinology. 2021;162:bqab154.
34. Aitken RJ. The changing tide of human fertility. Hum Reprod. 2022;37:629-38.
35. Gonsioroski A, Mourikes VE, Flaws JA. Endocrine disruptors in water and their effects on the reproductive system. Int J Mol Sci. 2020;21:1929.
36. Levine H, Jørgensen N, Martino-Andrade A, Mendiola J, Weksler-Derri D, Jolles M, et al. Temporal trends in sperm count: a systematic review and meta-regression analysis of samples collected globally in the 20th and 21st centuries. Hum Reprod Update. 2023;29:157-76.
37. Lokeshwar SD, Patel P, Fantus RJ, Halpern J, Chang C, Kargi AY, et al Decline in serum testosterone levels among adolescent and young adult men in the USA. Eur Urol Focus. 2021;7:886-9.
38. Chiaffarino F, Cipriani S, Dalmartello M, Ricci E, Esposito G, Fedele F, et al. Prevalence of polycystic ovary syndrome in European countries and USA: a systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2022;279:159-70.
39. Jijin JS. Queer studies: from the roots up. J Crit Rev. 2020;7:10868-73.
40. Ganna A, Verweij KJ, Nivard MG, Maier R, Wedow R, Busch AS, et al. Large-scale GWAS reveals insights into the genetic architecture of same-sex sexual behavior. Science. 2019;365:eaat7693.
41. Darbre PD. What are endocrine disrupters and where are they found? In: Endocrine Disruption and Human Health. United States: Academic Press; 2022. p. 3-29.
42. Aksoy Y, Basso HS, Smith RP, Grasl T. Demographic structure and macroeconomic trends. Am Econ J Macroecon. 2019;11:193-222.
43. Reher DS. The aftermath of the demographic transition in the developed world: interpreting enduring disparities in reproductive behavior. Popul Dev Rev. 2021;47:475-503.
44. Tudor S. Financial incentives, fertility and early life child outcomes. Lab Econ. 2020;64:101839.
45. Eichinger J, Eichinger T. Procreation machines: ectogenesis as reproductive enhancement, proper medicine or a step towards posthumanism? Bioethics. 2020;34:385-91.

Revista Médica del
Hospital General de México

PERMANYER

Check for updates

CLINICAL CASES

Medically refractory Mondor's disease of the penis

Hugo Rivera-Astorga[1], María P. Vázquez-Tabares[1], Paulina L. León-López[1], Ángel Gurrola-Ortega[1], Jorge Jaspersen-Gastelum[1], José F. Virgen-Gutiérrez[1], Eloy Rico-Frontana[1], and César A. Rivera-Colín[2]*

[1]Urology Service, Hospital General de México Dr. Eduardo Liceaga, Secretaría de Salud; [2]Department of Reconstructive Urology, Faculty of Medicine, Universidad Nacional Autónoma de México. Mexico City, Mexico

Abstract

The case involves a 24-year-old male diagnosed with Mondor's disease, with a duration of 3 months and resistance to anti-inflammatory pharmacological treatment. The decision is made to pursue surgical management through the resection of the dorsal vein of the penis. Mondor's disease typically exhibits self-limiting characteristics. Surgical intervention is considered when the patient proves resistant to conservative treatment after 8 weeks. It is essential to opt for a minimally invasive surgical approach to mitigate complications such as fibrosis or erectile pain, thereby enhancing the patient's quality of life.

Keywords: *Mondor's disease. Treatment-resistant. Surgical intervention.*

Introduction

Mondor's disease is defined as thrombophlebitis of the superficial veins of the dorsum of the penis[1]. Braun-Falco first reported isolated phlebitis in the dorsal vein of the penis in 1858[2], but the disease is named after Henri Mondor, a French surgeon responsible for describing a series of cases of thoracoepigastric vein thrombosis in female patients in 1939[3,4].

It manifests acutely as a subcutaneous indurated band that generates regional pain and episodic palpitations[5]; it is generally self-limiting in a range of 4-8 weeks[6]. It is an uncommon condition, with unknown pathophysiology, although there are hypotheses that indicate that the most common etiology is inflammation of the venous drainage of the penis together with Virchow's triad secondary to surgeries in the region, genital trauma, neoplasms, excessive exercise[7] blood stasis due to prolonged erection, vigorous sexual activity, bladder overdistension, and use of PDE inhibitors[5,6].

It affects sexually active men between 18 and 70 years of age, its incidence is 1.39% in a population between 20 and 40 years of age[8]; although it is believed to be higher, it is underdiagnosed because patients do not seek medical attention due to stigma[9]. The diagnosis is clinical, confirmed with Doppler ultrasound, where the main finding is the thrombosed vein in grayscale with the absence of flow; magnetic resonance angiography is also an option to confirm the diagnosis, as the venous network of the dorsum of the penis is dilated[10,11].

Treatment aims to control pain and reduce inflammation; non-steroidal anti-inflammatory drugs are widely used[1]. In addition to sexual abstinence, anticoagulant drugs, such as heparin, may be given in the acute phase of the disease[6].

Case report

A 24-year-old male patient with a history of epilepsy was treated with magnesium valproate and the rest of

***Correspondence:**
Hugo Rivera-Astorga
E-mail: hugolch_9@hotmail.com

Date of reception: 08-01-2024
Date of acceptance: 16-04-2024
DOI: 10.24875/HGMX.24000003

Available online: 01-04-2025
Rev Med Hosp Gen Mex. 2025;88(2):96-98
www.hospitalgeneral.mx

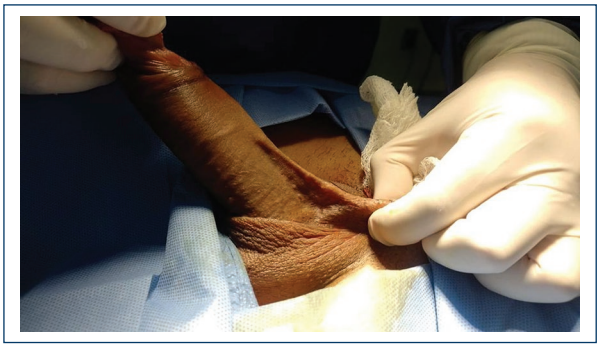


Figure 1. Stone band and curling on the back of the penis, shows fibrosis on the back of the penis one from the base.

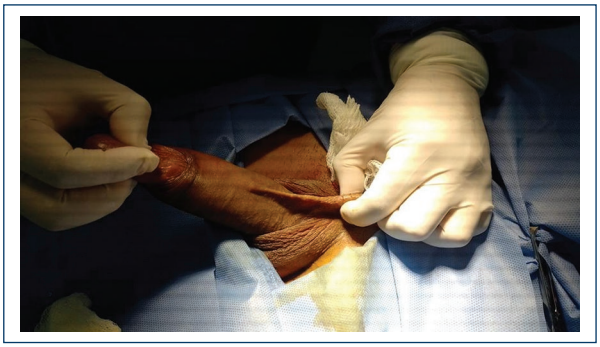


Figure 2. Stone band and curling on the back of the penis, showing the total length from the base to the balanopreputial groove.

the history was denied. For 3 months before his evaluation, he has had localized pain in the dorsum of the penis that is exacerbated by morning erections and at the time of urination due to the manipulation of the penis, sexual abstinence in this period due to pain.

She received previous treatment with antiplatelet and phlebotonics without any improvement, in addition to non-steroidal anti-inflammatory drugs without response; physical examination reveals stony and rosy tissue, which runs from the base of the penis and continues along the entire dorsum of the penis to the balanopreputial sulcus (Figs. 1 and 2). Resection of the superficial vein of the dorsum of the penis was performed with histopathological findings of thrombophlebitis, vein fragments with thrombi in the recanalization phase and fibrosis of the intima and hypertrophy of the muscle; and focally infiltrate chronic inflammatory lymphocyte in the intima and tunica media (Figs. 3 and 4).

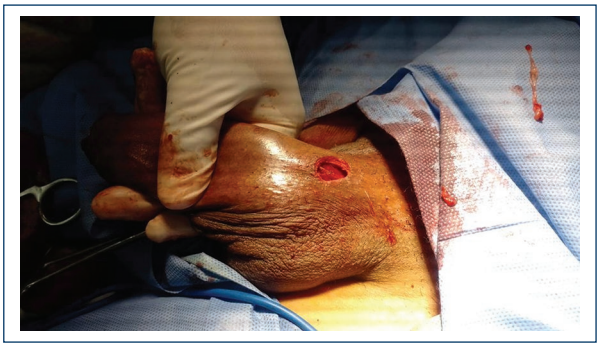


Figure 3. Proximal incision of the surgical approach.

Discussion

The cases reported in the literature found a benign condition as the most frequent cause of superficial thrombosis of the dorsal vein of the penis[12], the risk factor associated with the patient was vigorous sexual activity. Conservative medical treatment is the first option, consisting of sexual abstinence, pain relief, and control of inflammation with non-steroidal anti-inflammatory drugs; in addition, the improvement of circulation, only in the case of patients with underlying hypercoagulability problems with phlebotonics and anticoagulant. However, when thrombophlebitis persists for more than 8 weeks due to failure in first-line management, surgical correction based on resection of the superficial vein of the penis is resorted to.

In the reported case, a proximal and distal approach was performed, a procedure similar to performing a saphenectomy, with the aim of performing a minimally invasive surgery that does not compromise the patient's sexual functioning and performance due to complications such as pain in erection and fibrosis of the penis. In 2009, Salmon et al.[13] proposed a non-invasive technique to solve Mondor's disease, manual axial distraction, which provides patients with a fast, effective solution without adverse effects; it consists of applying firm pressure with distraction to several points of the thrombosed vein until the tension is overcome.

Prognosis depends on the underlying disease that led to dorsal penile vein thrombophlebitis; a report by Özkan in 2015 with 30 patients resolved with medical treatment reported that no permanent deformity of the penis or erectile dysfunction was found during the follow-up of the cases. Our patient had a satisfactory evolution with morning erections and the beginning of sexual life at 6 weeks.

Conclusion

It is a rare condition that is usually self-limiting and only requires pharmacological treatment. The choice of

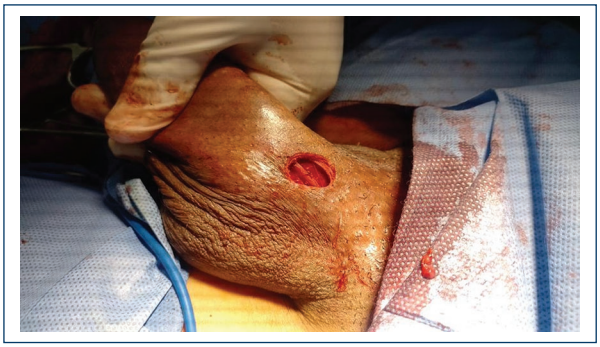


Figure 4. Proximal incision of the surgical approach.

surgical treatment is made when the patient is resistant to conservative treatment after 8 weeks; surgical management should be less invasive to avoid complications such as fibrosis or erection pain and consequently improve the patient's quality of life.

Funding

The authors declare that the work was funded by the Hospital General de México and the Urology Service.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Walsh JC, Poimboeuf S, Garvin DS. A common presentation to an uncommon disease. Penile Mondor's disease: a case report and literature review. Int Med Case Rep J. 2014;7:155-7.
2. Kumar B, Narang T, Radotra BD, Gupta S. Mondor's disease of penis: a forgotten disease. Sex Transm Infect. 2005;81:480-2.
3. Nazir SS, Khan M. Thrombosis of the dorsal vein of the penis (Mondor's disease): a case report and review of the literature. Indian J Urol. 2010;26:431-3.
4. Pittaka M, Fotiou E, Dionysiou M, Polyviou P, Eracleous E, Andreopoulos D, et al. Penile Mondor's disease in a patient treated with radical chemoradiation for anal cancer. Oxford Med CaseRep. 2017;2017:omx036.
5. Öztürk H. Penile Mondor's disease. Basic Clin Androl. 2014;24:5.
6. Amano M, Shimizu T. Mondor's disease: a review of the literature. Intern Med. 2018;57:2607-12.
7. Kraus S, Lüdecke G, Weidner W. Mondor's disease of the penis. Urol Int. 2000;64:99-100.
8. Foresti M, Parmiggiani A. Penile Mondor's disease: imaging in two cases. J Radiol Case Rep. 2020;14:24-30.
9. Boscolo-Berto R, Iafrate M, Casarrubea G, Ficarra V. Magnetic resonance angiography findings of penile Mondor's disease. J Magn Reson Imaging. 2009;30:407-10.
10. Gahlawat S, Gupta D, Kumar A, Sood R. Surgical management of penile Mondor's disease: case report and brief review of literature. Indian J Case Rep. 2022;5:137-9.
11. Rodríguez Faba O, Parra Muntaner L, Gómez Cisneros SC, Martín Benito JL, Escaf Barmadah S. Trombosis de la vena dorsal del pene (Flebitis de Mondor). Aportación de un nuevo caso. Actas Urol Esp. 2006; 30:80-2.
12. Linden-Castro E, Pelayo-Nieto M, Ramirez-Galindo I, Espinosa-Perezgrovas D, Cornejo-Davila V, Rubio-Arellano E. Mondor disease: thrombosis of the dorsal vein of the penis. Urol Case Rep. 2018;19:34-5.
13. Salmon RJ, Berry M, Hamelin JP. A novel treatment for postoperative Mondor's disease: manual axial distraction. Breast J. 2009;15:381-4.

Revista Médica del
Hospital General de México

PERMANYER

Check for updates

CLINICAL CASES

Spigelian hernia, a case series of four cases and literature review

Carlos O. Fonseca-Bravo[1], Edwin R. Novelo[1], and Hugo de J. Castellanos[2]*

[1]Department of General Surgery, Hospital San Carlos, Tizimin, Yucatán; [2]Department of General Surgery, Hospital de Especialidades No. 14, Centro Médico Nacional Adolfo Ruiz Cortines, Instituto Mexicano del Seguro Social, Veracruz, Veracruz. Mexico

Abstract

Four female patients aged 50-85 underwent surgery for Spiegel hernia. One patient was managed with antibiotics for 2 weeks before presenting to the emergency department with non-specific symptoms and signs of sepsis. Emergency laparoscopic surgery was converted to laparotomy due to the discovery of pus and appendicitis. The abdominal defect was closed using a tension technique to mitigate the risk of mesh infection. This patient recovered well and was discharged after 36 h with a double antibiotic regimen. Three elective surgeries utilized an open approach with different mesh placement techniques and resulted in discharges within 24 h. These cases demonstrate diverse surgical approaches and outcomes in older female patients.

Keywords: *Spiegel. Hernia. Appendicitis. Rives.*

Introduction

Ventral lateral hernia, interstitial hernia, and interparietal hernia, better known as Spiegel's hernias, are a rare condition (0.1-2% of all abdominal wall hernias), in which there is a defect in the transversus aponeurosis on the semilunar line, with frequently a hernial sac sliding below the intact external oblique aponeuroses, it is often externalized at the weak point located at the intersection between the semilunar line and the lateral end of the arched line, In a transition zone of the posterior rectus abdominis aponeurosis[1]. These hernias occur most frequently in patients between the sixth and seventh decade, with no significant difference in the incidence between genders. Surgical resolution may be with an open approach, frequently using the Rives technique, or with a laparoscopic approach with an extraperitoneal or transperitoneal technique.

Cases report

Case 1

An 85-year-old female with a history of chronic systemic hypertension treated with telmisartan, which came to us through the emergency department because of 15 days of abdominal pain referred in the lower abdomen, treated firstly in another clinic with antibiotics (ceftriaxone) and non-steroidal anti-inflammatory drugs, with transient relief, reason why she seeks attention in San Carlos General Hospital. After interrogation and physical examination in which right quadrant and low abdomen tenderness were recognized, blood tests were requested with the following results: Leukocytes 21.5 × 10^3/mm^3, neutrophils 81%, hemoglobin 10.2 g/dL, hematocrit 30.8%, platelets 206 × 10^3/mm^3, prothrombin time 13.8, partial thromboplastin time 23.4 seg,

***Correspondence:**
Carlos O. Fonseca-Bravo
E-mail: fonsecacarlos91@gmail.com

Date of reception: 27-10-2023
Date of acceptance: 06-05-2024
DOI: 10.24875/HGMX.23000083

Available online: 01-04-2025
Rev Med Hosp Gen Mex. 2025;88(2):99-103
www.hospitalgeneral.mx

international normalized ratio 1.31, and C reactive protein 170 mg/L. The patient goes through a diagnostic laparoscopy finding an incarcerated Spigelian hernia with a portion of the right wall of the bladder and complicated appendicitis (Fig. 1). Due to a lack of materials, the procedure is converted to a laparotomy, reducing the contents of the hernia, doing an appendicectomy and ventral closure of the Spigelian belt defect. A Penrose drainage to the pelvis is inserted, which in subsequent days showed no signs of abdominal complication. The patient starts with a liquid diet the next morning after the surgery, later on a normal diet is given, with no throwback. The patient is able to walk; Penrose is extracted and after no clinical manifestation of complication, is sent home 48 h post-surgery.

The other three patients came to us through the surgery consult because of vague and unspecific symptoms, two patients were diagnosed with chronic cholecystitis before our visit, because of gallbladder stones in ultrasound, being ruled out after an appropriate questioning and physical examination and mainly because abdominal pain was in the lower abdomen and differed totally from typical pain referred by chronic cholecystitis patients. They all referred to mild, intermittent abdominal pain related to a mass in the low right or left quadrant. This mass, as described by two patients, spontaneously disappeared when in decubitus and came back on when standing or seated.

Case 2

A 53-year-old female, with a clinical background of bilateral tubal oophorectomy in 2011, right inguinal repair with mesh in 2016, and chronic hypertension treated with losartan, with a 3-year history of a mass in the low left quadrant of the abdomen, with episodes of pain and bulking. The abdominal Ultrasound (Fig. 2) came back reporting: a gallbladder with 72 × 19 mm measure, thin walls, with a single stone inside, and a left Spiegel's hernia of 17 × 13 mm. Surgery was done on August 29, 2022, where a 6 cm Spiegel's hernia was found with omentum (Fig. 3) on its inside, with an aponeurosis defect of 3 cm in the transversalis and minor oblique muscle, being both aponeuroses repaired with a smead jones closure using a vycril suture, and mesh placement in between the major and minor oblique in a Rives fashion way. She is dismissed 24 h post-surgery, with adequate oral tolerance and painlessness.

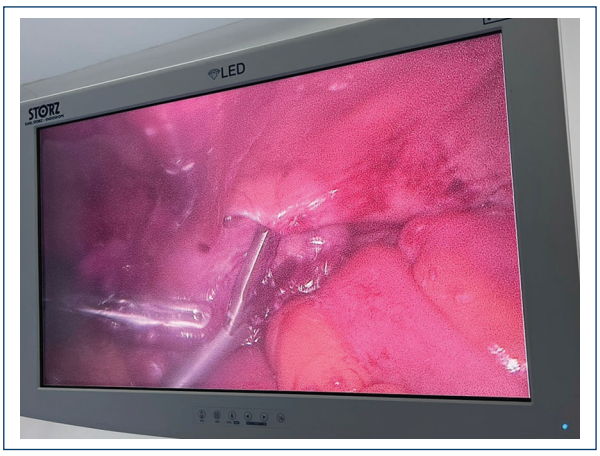


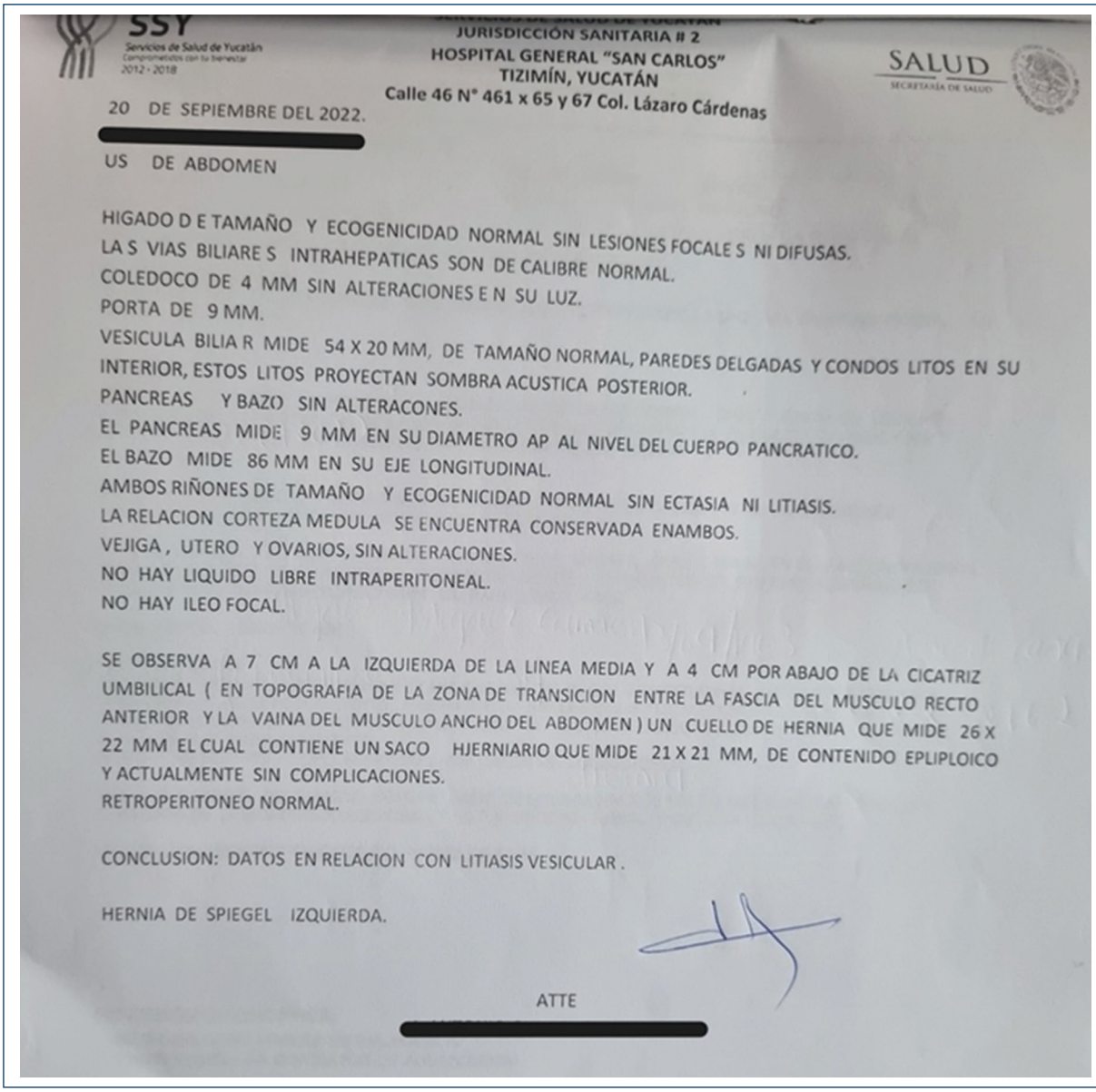
Figure 1. Diagnostic laparoscopy finds pus at the right lower quadrant.

Case 3

A 59-year-old female with a background of cesarean delivery and BTO, anxiety and depression disorder treated with clonazepam and risperidone, with a history of 6 months of biliary colic, with an abdominal Ultrasound reporting: gallbladder with 54 × 20 mm measurement, thin walls and two stones on its inside, 7 cm to the left of the abdominal midline (at the transition zone between the rectus anterior muscle fascia and the oblique muscle sheath) a hernia neck measuring 26 × 22 mm which contains a hernial sac measuring 21 × 21 mm of omental content. We decided to treat the hernia first. The patient was intervened on October 17, 2022, finding a 4 cm hernia defect in transversalis muscle, with a 5 cm protruding sac with omentum on its inside (Fig. 4). The defect is treated with a Rives fashion mesh in the pre-peritoneal space after careful dissection, minor oblique aponeurosis is closed with a continued vycril suture, so as the major oblique aponeurosis, skin is closed with a subdermal suture with nylon 3-0. The patient is dismissed 24 h post-surgery, with no complications.

Case 4

A 68-year-old female, who comes as an outpatient appointment in October 2022, with a clinical background of 20 years evolution diabetes type 2 and two cesarean deliveries with an infraumbilical approach, complaining of a 5-month diffuse abdominal pain in the lower abdomen, without a mass. At the physical examination of the right lower abdomen, at the Spiegels belt, a palpable abdominal mass, which reduces with



SSY
Servicios de Salud de Yucatán
Comprometidos con tu bienestar
2012 - 2018

JURISDICCIÓN SANITARIA # 2
HOSPITAL GENERAL "SAN CARLOS"
TIZIMÍN, YUCATÁN
Calle 46 N° 461 x 65 y 67 Col. Lázaro Cárdenas

SALUD
SECRETARÍA DE SALUD

20 DE SEPIEMBRE DEL 2022.

[redacted]

US DE ABDOMEN

HIGADO D E TAMAÑO Y ECOGENICIDAD NORMAL SIN LESIONES FOCALE S NI DIFUSAS.
LA S VIAS BILIARE S INTRAHEPATICAS SON DE CALIBRE NORMAL.
COLEDOCO DE 4 MM SIN ALTERACIONES E N SU LUZ.
PORTA DE 9 MM.
VESICULA BILIA R MIDE 54 X 20 MM, DE TAMAÑO NORMAL, PAREDES DELGADAS Y CONDOS LITOS EN SU INTERIOR, ESTOS LITOS PROYECTAN SOMBRA ACUSTICA POSTERIOR.
PANCREAS Y BAZO SIN ALTERACONES.
EL PANCREAS MIDE 9 MM EN SU DIAMETRO AP AL NIVEL DEL CUERPO PANCRATICO.
EL BAZO MIDE 86 MM EN SU EJE LONGITUDINAL.
AMBOS RIÑONES DE TAMAÑO Y ECOGENICIDAD NORMAL SIN ECTASIA NI LITIASIS.
LA RELACION CORTEZA MEDULA SE ENCUENTRA CONSERVADA ENAMBOS.
VEJIGA , UTERO Y OVARIOS, SIN ALTERACIONES.
NO HAY LIQUIDO LIBRE INTRAPERITONEAL.
NO HAY ILEO FOCAL.

SE OBSERVA A 7 CM A LA IZQUIERDA DE LA LINEA MEDIA Y A 4 CM POR ABAJO DE LA CICATRIZ UMBILICAL (EN TOPOGRAFIA DE LA ZONA DE TRANSICION ENTRE LA FASCIA DEL MUSCULO RECTO ANTERIOR Y LA VAINA DEL MUSCULO ANCHO DEL ABDOMEN) UN CUELLO DE HERNIA QUE MIDE 26 X 22 MM EL CUAL CONTIENE UN SACO HJERNIARIO QUE MIDE 21 X 21 MM, DE CONTENIDO EPLIPLOICO Y ACTUALMENTE SIN COMPLICACIONES.
RETROPERITONEO NORMAL.

CONCLUSION: DATOS EN RELACION CON LITIASIS VESICULAR .

HERNIA DE SPIEGEL IZQUIERDA.

ATTE

[redacted]

Figure 2. Detailed description of the diagnosis of Spiegelian hernia.

pressure, with no referred pain at manipulation. USG: In the right iliac fossa, at inguinal height, below subcutaneous cell tissue a round-shaped image that measures 32 × 14 mm, which increases with Valsalva, to 38 × 20 mm. She was surgically intervened on December 12, 2022, finding a 6 cm defect on the transversalis fascia, with a protruding sac with omentum on its inside, placing the mesh in the pre-peritoneal space (Fig. 5) after careful dissection in a plug and mesh fashion, minor and major oblique aponeurosis is closed separately with a vycril suture, skin is closed in a subdermal suture with nylon 3-0. The patient is dismissed after 24 h with no complications.

Discussion

Most hernias thus occur at the level of the Spigelian girdle, an area 6 cm high situated between the umbilicus at the top and a line passing through the anterior superior iliac spines at the bottom[2].

Spiegel's hernia represents a diagnostic challenge for the surgeon due to its low incidence rate and unspecific symptoms if there are any. If the patient has a palpable lump along the Spigelian aponeurosis, the diagnosis is apparent. The same applies if the hernia appears when the patient is upright and disappears spontaneously on lying down. The clinical diagnosis of

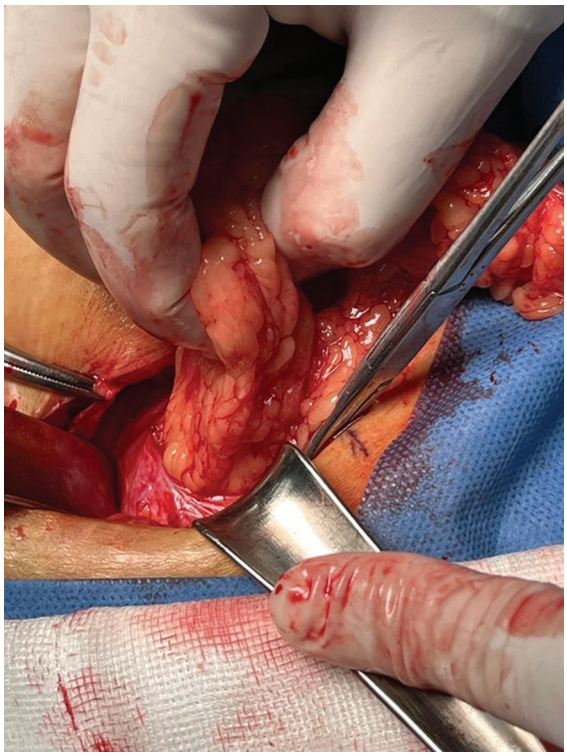


Figure 3. Omentum inside the defect of the transversus abdominis fascia. In Kelly grasps, major oblique aponeurosis.

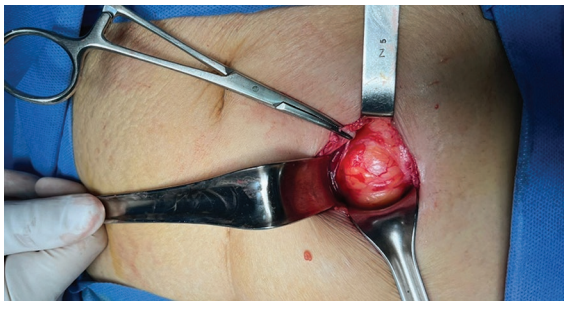


Figure 4. Weakening of the abdominal wall, underneath the major oblique aponeurosis (grasped by Kelly). To the left of the image, the umbilicus.

hernia is complicated by that the defect continues to expand laterally and caudally between two oblique muscles[3]. Patients usually may be asymptomatic, or even present to consultation for a different condition as presented above. Some of the symptoms referred by patients with a ventral lateral hernia include mild abdominal pain (more often while standing or walking) or may feel a mass (which may disappear in decubitus),

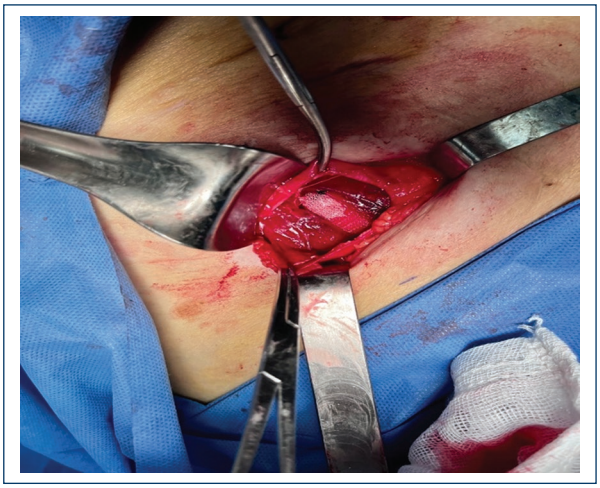


Figure 5. Major oblique aponeurosis grasped by Kelly clamp. Below, mesh in a plug-and-mesh fashion to repair the hernia.

which the surgeon needs to keep a high suspicion in mind while facing these patients because of the low incidence and the ambiguous symptoms. The usefulness of ultrasound and computed tomography is emphasized, especially in cases in which the clinical presentation can be confusing[4].

Treatment is surgical; different approaches are feasible: direct, by raphy or pre-peritoneal or pre-aponeurotic prosthetic replacement; laparoscopic, by intra-peritoneal, trans-abdominal pre-peritoneal or extra-peritoneal raphy or mesh repair. If the hernial ring is narrow (< 2 cm) A direct approach herniorrhaphy is usually sufficient. Otherwise, a laparotomy approach or transperitoneal laparoscopic repair with a double-sided or pre-peritoneal mesh is performed, with a lower risk of recurrence with synthetic mesh than simple suture[5].

Conclusion

Spiegel's hernia, as cited above, is a very rare condition which we had the opportunity to treat in four different cases in a relatively short period of time for its incidence, including an emergency case associated with appendicitis, making it even rarer.

Acknowledgments

The authors would like to thank the patients for letting us treat them, and contributing to our professional growth.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Moszkowicz D, Paye F, Balladur P, Lefevre JH. Une cause rare d'occlusion aiguë du grêle : la hernie de Spiegel étranglée. Description d'un cas et revue de la littérature. Morphologie. 2012;96:12-5.
2. Mittal T, Kumar V, Khullar R, Sharma A, Soni V, Baijal M, et al. Diagnosis and management of spigelian hernia: a review of literature and our experience. J Minim Access Surg. 2008;4:95-8.
3. Skandalakis PN, Zoras O, Skandalakis JE, Mirilas P. Spigelian hernia: surgical anatomy, embryology, and technique of repair. Am Surg. 2006;72:42-8.
4. Aguilar OG, Sarotto LE, Corti M, Allevato MÁ, Palermo Obstetricia MS, Lemus Epidemiología JD, et al. Hernia semilunar estrangulada. Presentación de un caso. Available from: https://prensamedica.com.ar/LPMA_V107_N05_comp.pdf [Last accessed on 2023 Jan 03].
5. Bouali M, El Attar L, Elhattabi K, Elbakouri A, Bensardi F, Fadil A. Strangulated spiegel hernia: about a case and literature review. Ann Med Surg (Lond). 2021;66:102453.

Revista Médica del
Hospital General de México

PERMANYER

Check for updates

CLINICAL CASES

Auditory neuropathy spectrum disorder in a patient with normal hearing and its medical management: case presentation and literature review

Jesús A. Silva-Rojas[1,2], Karla L. Ruiz-Lira[1], Emilio Dávalos-González Plata[1], and Pablo A. Ysunza-Rivera[2]*

[1]Audiology and Phoniatrics Service, Unidad 601, Hospital General de México Dr. Eduardo Liceaga, Secretaría de Salud, Mexico City, Mexico; [2]Neuroscience Program, Ian Jackson Craniofacial and Cleft Palate Clinic, Beaumont Health, Royal Oak, MI, USA

Abstract

Auditory neuropathy spectrum disorder (ANSD) is a group of alterations of the auditory system that manifests the presence of otoacoustic emissions and the absence of responses in auditory brainstem response. However, because these patients can have a very diverse clinical presentation, their management is very complex. Patients can present from normal hearing with practically normal development, to profound hearing loss with various comorbidities that require a highly individualized approach. Early detection and close follow-up of ANSD should be a priority to avoid iatrogenic management.

Keywords: *Auditory neuropathy spectrum disorder. Auditory brainstem response. Otoacoustic emissions. Automated auditory brainstem response.*

Introduction

Auditory neuropathy spectrum disorder (ANSD) is thought to be a set of alterations in the auditory system that can include alterations in the synapses of the inner hair cells of the cochlea, or alterations of the spiral ganglion, or myelination defects of auditory nerve axons, or defects in the cochlear nuclei and even a varying degree of involvement of all the aforementioned factors[1]. This spectrum has shown a diagnostic boom from the establishment of early hearing detection programs, such as the performance of otoacoustic emissions (OAE), automated auditory potentials such as neonatal hearing screening tests, and the short-latency auditory provoked potential (SLAEP) test for diagnostic confirmation[2]. Typically, patients with ANSD have present OAEs and absent or seriously altered auditory potentials in all its variants, including SLAEP and PPA, as well as the cochlear microphone response that changes polarity when the polarity of the provocative stimulus changes in the SLAEP[3]. On the other hand, in these patients, the real auditory threshold, or behavioral threshold, can only be determined by behavioral studies such as tonal audiometry in all its variants, including pediatric variants[4]. To reiterate, no electrophysiological study provides reliable hearing threshold answers if ANSD is present. However, audiological studies in a population under 3 years of age must be performed by highly trained, experienced personnel, ideally requiring two specialists for each study/patient, and taking considerable time, and sometimes even several appointments

***Correspondence:**
Jesús A. Silva-Rojas
E-mail: asrmx1@gmail.com

Date of reception: 14-03-2024
Date of acceptance: 13-05-2024
DOI: 10.24875/HGMX.24000021

Available online: 01-04-2025
Rev Med Hosp Gen Mex. 2025;88(2):104-109
www.hospitalgeneral.mx

to reach an audiometric diagnosis. In addition, these studies cannot be reliably performed in children under 6 months of age, and there is a great deal of subjectivity in detecting audiometric thresholds in this age group[5]. A serious problem with this population of pediatric patients with ANSD is that the audiometric thresholds can range from normal hearing to profound hearing loss, likewise, language discrimination can range from normal (100%) to 0%. Evolution is unpredictable and must be monitored very closely with feedback obtained from parents or guardians, and even teachers if necessary[6].

Hearing screening in all cases should ideally be performed with automated potentials (PPA) in both normal pediatric and pediatric populations with high hearing risk. This screening test can not only detect normal hearing or hearing loss in an infant due to cochlear or middle and outer ear damage but also the electrophysiological alteration of the recordings produced by ANSD in the auditory pathway. Unlike OAEs that do not evaluate the auditory pathway and may be normal in ANSD[7]. Because the prevalence/total incidence of ANSD is significantly low in the open population of apparently normal newborns, the use of OAE is widely used to perform neonatal hearing screening, since the possibility of referring a child with ANSD as normal is considered very low[8]. Moreover, the performance of the two tests, SLAEP and OAE, is only indicated in children with high auditory/neurological risk since, as is known, the incidence of this pathology increases considerably in them. Unlike PPAs, SLAEPs are not routinely performed on healthy children because they require specialized personnel for their execution and interpretation, and the time is considerable unlike hearing screening tests, OAEs, and PPAs, which can be obtained in seconds to a few minutes[9].

Patients with ANSD, although with studies of otoacoustic and neurophysiological emissions that are practically the same among all patients, as already mentioned, may present an unpredictable evolution, as well as a very varied clinical picture, and there may be adult patients with difficulty hearing noise, but otherwise normal. Moreover, children with profound hearing loss, multiple comorbidities, and the need for a multidisciplinary approach may even reach cochlear implantation[1,3,9].

ANSD is believed to be multifactorial and can occur in an open population without any apparent neurological or auditory risk factors. On the other hand, it can occur in populations with high audiological or neurological risk, it has even been described as a sequel of Guillain–Barré syndrome or in patients with later-onset neurological diseases such as patients with Freidreich's ataxia[10].

In the open population, ANSD has an unknown frequency in apparently healthy adults. The prevalence of auditory neuropathy varies and can range from 1% to 10% of individuals who have hearing loss, and in newborns with auditory risk factors at birth, the prevalence can reach up to 30%. The prevalence is higher in the pediatric population than in adults[11-14].

Infants with ANSD should not be adapted with hearing aids or cochlear implants due to the absence of responses in SALP and PPA due to the possibility that despite the presence of ANSD they have normal hearing[15]. In these cases, it is suggested that they are frequently cited with the idea of closely monitoring psychomotor development, language development, and auditory behavior reported by the parents[16]. Since, a patient with ANSD without complete studies when simulating profound hearing loss and being adapted with hearing aids runs the risk of presenting irreversible damage at the cochlear level due to exposure to intense sound and consequently losing that valuable function, thus complicating the picture by iatrogenesis. In general, when the parent or guardian is involved, they can provide invaluable information that the specialist can interpret appropriately to improve their diagnosis and individual management according to the evolution of each case[1,6-9].

The purpose of this article is to present a case of a child with ANSD initially diagnosed as hearing loss and with follow-up, who showed electrophysiological improvement *ad integrum* of ANSD.

Case presentation

A female patient born prematurely at 33.4 weeks of gestation with respiratory distress syndrome, pulmonary bronchodysplasia, low birth weight, and anemia of prematurity. There was a risk of sepsis due to a positive maternal history of urine culture for *Enterococcus faecalis*. Placenta previa was identified due to the presence of transvaginal bleeding and a Kerr-type cesarean section was performed at 33.4 weeks of gestation. Apgar from 7 at 1 min and 8 at 5 min. Silvermann of 4. Respiratory whine and thoracoabdominal dissociation treated with CPAP for 72 h did not meet the criteria for asphyxia. She was admitted to the neonatal intensive care unit due to respiratory history and

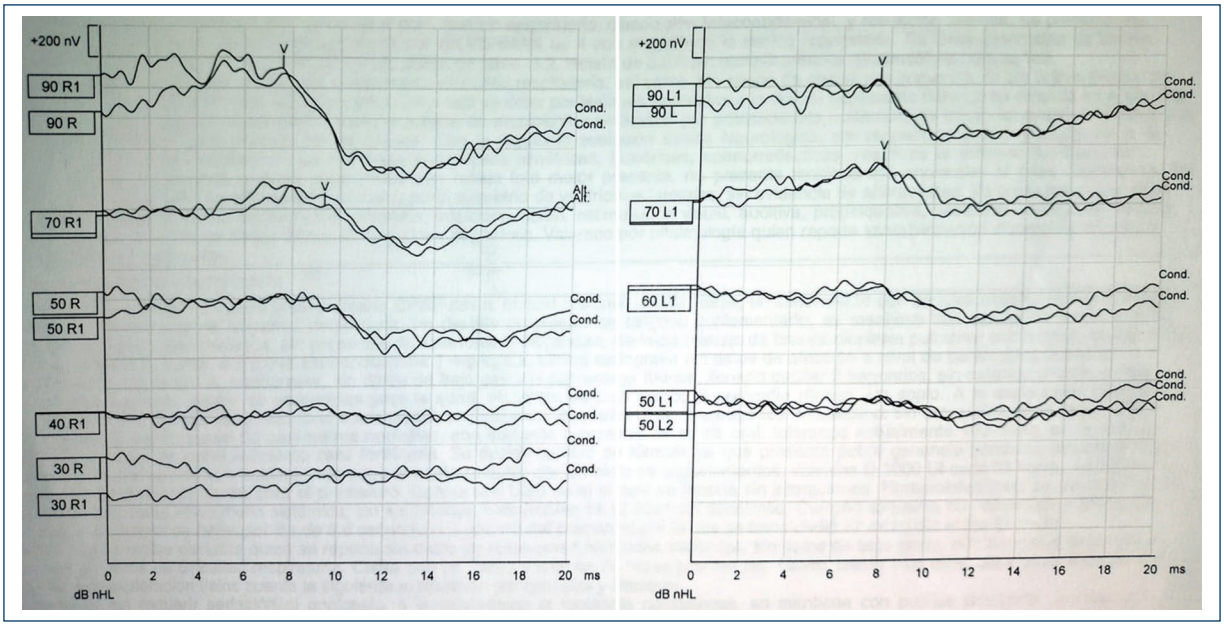


Figure 1. A record of SLAEP was performed at 12 weeks extrauterine, showing poor amplitude, altered morphology, and V-wave with an apparent threshold of 50 dBnHL.

probable sepsis. She received ampicillin, amikacin, fluticasone aerosol, spironolactone, and a blood transfusion. In total, she was hospitalized for 48 days and was discharged. A neonatal hearing screening was performed during her hospital stay, and a normal result was found; however, she was referred to the Audiology and Phoniatrics Service of the Hospital General de México for complementary audiological evaluation due to her history of high hearing risk.

PPALC tests were performed with CE-Chirp stimulus at 3 months of extrauterine life, and SLAEP with V-wave at 50 dBnHL was found, which corresponds to medium-grade hearing loss (Fig. 1). However, when questioning the mother, she refers to an apparent auditory behavior of a hearing norm. For this reason, it was initially diagnosed as middle hearing loss, but the diagnostic protocol for auditory neuropathy was initiated. Again, a month after a month is scheduled to perform SLAEP, this time for cochlear microphone search with stimulus, tone burst with polarity, condensation, and rarefaction (Fig. 2) and to perform OAEs (Fig. 3). There was an inversion of the cochlear microphone with this change in polarity, so probe clamping was performed to rule out the artifact, and normal OAEs were identified. For this reason, ANSD is diagnosed and the mother is instructed to closely monitor auditory behavior, language development, and psychomotor development. Follow-up appointments are given 3 and 6 months later for monitoring of auditory behavior and language development, finding him within normal parameters. A new appointment is made for SLAEP, which is performed at 10 months of age, and V-wave responses are found at normal intensities (better than 30dBnHL) and neurological parameters of the SLAEP within normal limits (Fig. 4). The mother reports auditory behavior of a normal listener, language at the level of a single word, recognizes her relatives. An appointment is made in 6 months and the patient no longer attends. As of the day this article is written, she has not been followed up.

Discussion

As previously mentioned, hearing thresholds in patients with ANSD can vary from normal hearing to profound hearing loss depending on each patient[17], as is the case of this patient since the mother reported normal hearing due to behavioral response even to low-intensity sound stimuli from an early age and this is what has guided us for the successful management of this case. To inexperienced eyes, such a result in SLAEP could simulate hearing loss, the primary management of which would be auditory rehabilitation with hearing aids in both ears; however, it was decided to follow close expectant management. Even in patients already

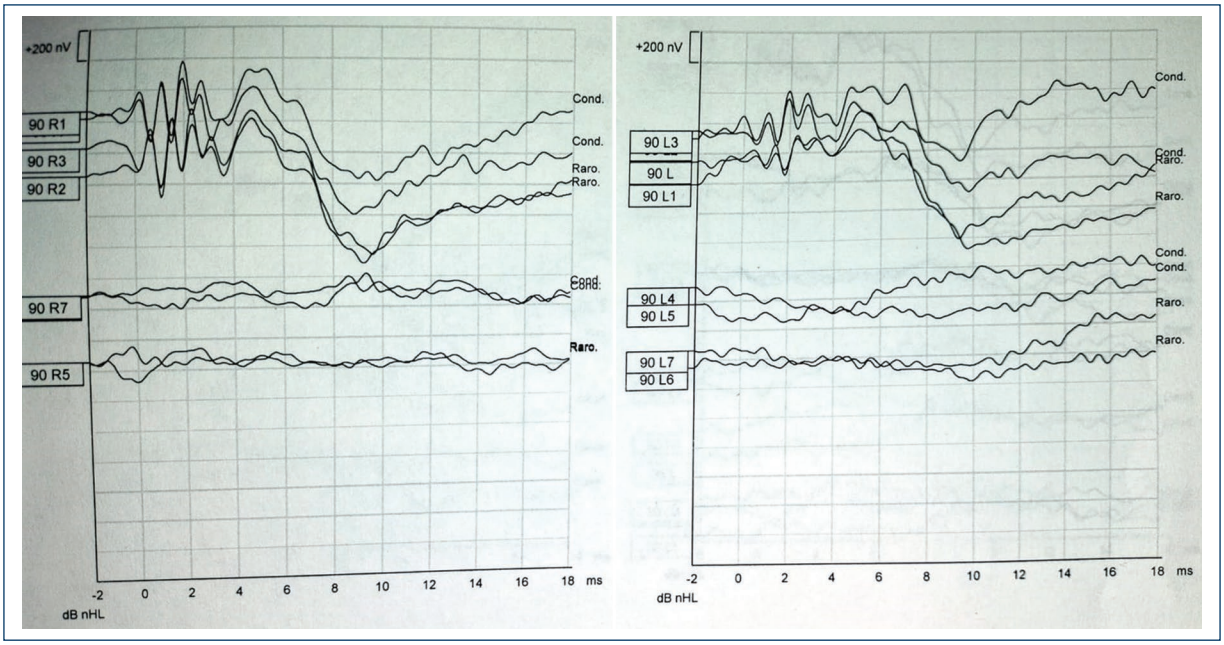
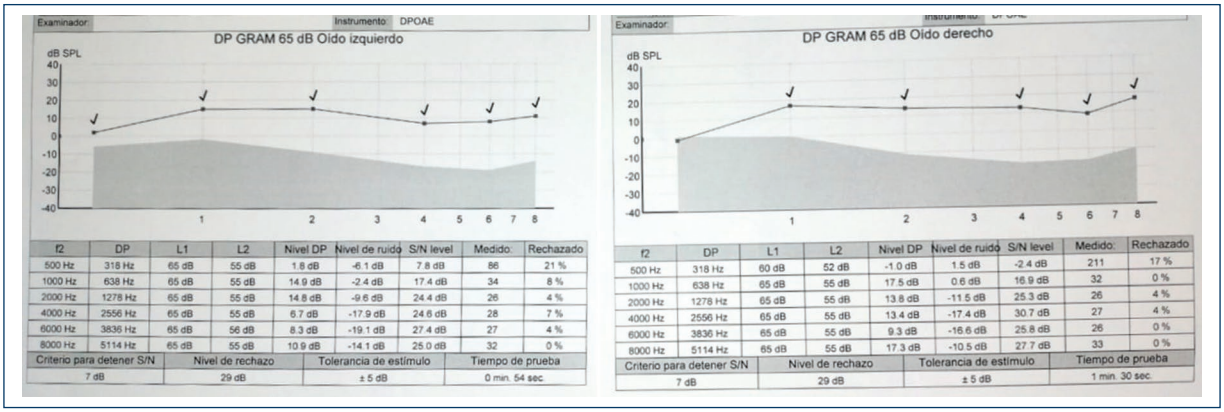


Figure 2. A record of SLAEP for cochlear microphone search was performed at 16 weeks of age with tone-burst, showing the microphone with phase inversion of 180º and below a clamping test where a total absence of responses was observed.



f2	DP	L1	L2	Nivel DP	Nivel de ruido	S/N level	Medido:	Rechazado
500 Hz	318 Hz	65 dB	55 dB	1.8 dB	-6.1 dB	7.8 dB	86	21 %
1000 Hz	638 Hz	65 dB	55 dB	14.9 dB	-2.4 dB	17.4 dB	34	8 %
2000 Hz	1278 Hz	65 dB	55 dB	14.8 dB	-9.6 dB	24.4 dB	26	4 %
4000 Hz	2556 Hz	65 dB	55 dB	6.7 dB	-17.9 dB	24.6 dB	28	7 %
6000 Hz	3836 Hz	65 dB	56 dB	8.3 dB	-19.1 dB	27.4 dB	27	4 %
8000 Hz	5114 Hz	65 dB	55 dB	10.9 dB	-14.1 dB	25.0 dB	32	0 %
Criterio para detener S/N		Nivel de rechazo		Tolerancia de estímulo			Tiempo de prueba	
7 dB		29 dB		± 5 dB			0 min. 54 sec.	

f2	DP	L1	L2	Nivel DP	Nivel de ruido	S/N level	Medido:	Rechazado
500 Hz	318 Hz	60 dB	52 dB	-1.0 dB	1.5 dB	-2.4 dB	211	17 %
1000 Hz	638 Hz	65 dB	55 dB	17.5 dB	0.6 dB	16.9 dB	32	0 %
2000 Hz	1278 Hz	65 dB	55 dB	13.8 dB	-11.5 dB	25.3 dB	26	4 %
4000 Hz	2556 Hz	65 dB	55 dB	13.4 dB	-17.4 dB	30.7 dB	27	4 %
6000 Hz	3836 Hz	65 dB	55 dB	9.3 dB	-16.6 dB	25.8 dB	26	0 %
8000 Hz	5114 Hz	65 dB	55 dB	17.3 dB	-10.5 dB	27.7 dB	33	0 %
Criterio para detener S/N		Nivel de rechazo		Tolerancia de estímulo			Tiempo de prueba	
7 dB		29 dB		± 5 dB			1 min. 30 sec.	

Figure 3. OAE recording of both ears, the schools show normal responses.

diagnosed with ANSD with tonal thresholds by behavioral methods, adaptation is difficult and has to be individualized with each patient[18]. Another rehabilitation route for patients with profound hearing loss is the cochlear implant, and it is very important to know that, in patients with auditory neuropathy, although the behavioral thresholds are of profound hearing loss, expectant management is suggested at least until 2 years of age[19], so if an adequate adaptation is not made. We could generate, as mentioned, irreversible iatrogenic cochlear damage.

Another reason for maintaining expectant management in the auditory rehabilitation of patients with ANSD is because it has been reported that some patients may present recovery in the morphology of the bioelectrical components of the SLAEP and even recovery from hearing loss[19], and although the prevalence in the general population has not been described, it is known to be more frequent in premature patients[19,20], so these patients have to be constantly monitored with SLAEP.

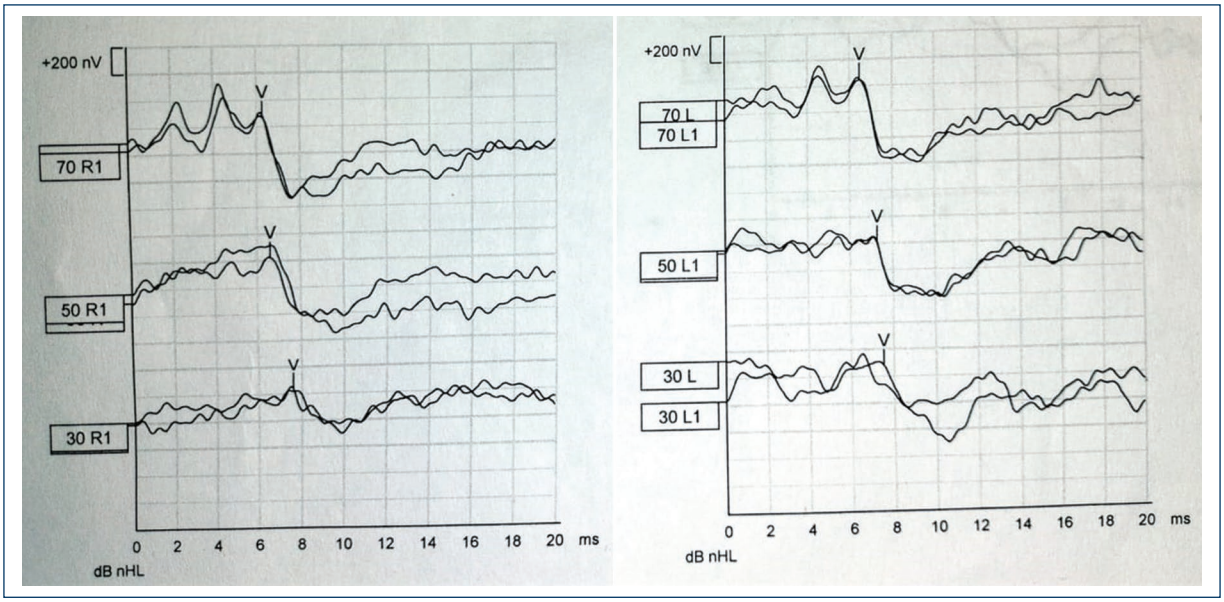


Figure 4. A 10-month record of SLAEP shows normal audiological and neurophysiological parameters.

Conclusion

All ANSD patients have in common absent or severely altered SLAEP, and present OAE, however the behavioral hearing threshold can only be determined by behavioral audiometric procedures, which is very difficult and unreliable to obtain in very young children. In ANSD behavioral thresholds can range from normal hearing to profound hearing loss. The only way to determine the need to adapt hearing aids in very young children is through the information the parents give us about speech development and auditory behavior, and frequent and close audiological surveillance as well.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from the patient's parents, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Starr A, Rance G. Auditory neuropathy. Hand Book Clin Neurol. 2015;129:495-508.
2. Van Straaten HL. Automated auditory brainstem response in neonatal hearing screening. Acta Paediatr Suppl. 1999;88:76-9.
3. Madden C, Rutter M, Hilbert L, Greinwald JH Jr., Choo DI. Clinical and audiological features in auditory neuropathy. Arch Otolaryngol Head Neck Surg. 2002;128:1026-30.
4. Baldwin SM, Gajewski BJ, Widen JE. An evaluation of the cross-check principle using visual reinforcement audiometry, otoacoustic emissions, and tympanometry. J Am Acad Audiol. 2010;21:187-96.
5. Sabo DL. The audiologic assessment of the young pediatric patient: the clinic. Trends Amplif. 1999;4:51-60.
6. Chinese Multi-center Research Collaborative Group on Clinical Diagnosis and Intervention of Auditory Neuropathy; Editorial Board of Chinese Journal of Otorhinolaryngology Head and Neck Surgery; Society of Otorhinolaryngology Head and Neck Surgery, Chinese Medical Association, China Division; International Association of Physicians in Audiology, Society of Audiology and Vestibular Medicine; China International Exchange and Promotive Association for Medical and Health Care. Chinese clinical practice guideline of auditory neuropathy (version 2022). Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2022;57:241-62.
7. Maris M, Venstermans C, Boudewyns AN. Auditory neuropathy/dyssynchrony as a cause of failed neonatal hearing screening. Int J Pediatr Otorhinolaryngol. 2011;75:973-5.
8. Bansal S, Gupta A, Nagarkar A. Transient evoked otoacoustic emissions in hearing screening programs: protocol for developing countries. Int J Pediatr Otorhinolaryngol. 2008;72:1059-63.
9. Kai U. Transient auditory neuropathy in infants: how to conceptualize the recovery of auditory brain stem response in the context of newborn hearing screening? Semin Hear. 2011;32:123-28.

10. López-Díaz de León E, Silva-Rojas A, Ysunza A, Amavisca R, Rivera R. Auditory neuropathy in friedreich ataxia. A report of two cases. Int J Pediatr Otorhinolaryngol. 2003;67:641-8.
11. Rance G, McKay C, Grayden D. Perceptual characterization of children with auditory neuropathy. Ear Hear. 2004;25:34-46.
12. Bielecki I, Horbulewicz A, Wolan T. Prevalence and risk factors for auditory neuropathy spectrum disorder in a screened newborn population at risk for hearing loss. Int J Pediatr Otorhinolaryngol. 2012;76:1668-70.
13. Kumar UA, Jayaram MM. Prevalence and audiological characteristics in individuals with auditory neuropathy/auditory dys-synchrony. Int J Audiol. 2006;45:360-6.
14. Muthukumar R, Jaya V, Vignesh SS, Thenmozhi K. Prevalence and auditory characteristics of auditory neuropathy spectrum disorder in adult population with sensory neural hearing loss: a hospital based study in South India. Indian J Otolaryngol Head Neck Surg. 2023;75:1906-11.
15. Sahwan M, Abdelsamad Y, Alasfoor F, Alfayez F, Binkhamis G, Nichani J. Cochlear implantation in children with auditory neuropathy spectrum disorder: an updated systematic review. Eur Arch Otorhinolaryngol. 2024;281:1149-62.
16. Morlet T, O'Reilly R, Pritchett C, Venskytis E, Parkes W. A 15-year review of 260 children with auditory neuropathy spectrum disorder: II. Management and outcomes. Ear Hear. 2023;44: 979-89.
17. De Siati RD, Rosenzweig F, Gersdorff G, Gregoire A, Rombaux P, Deggouj N. Auditory neuropathy spectrum disorders: from diagnosis to treatment: literature review and case reports. J Clin Med. 2020; 9:1074.
18. Sharma A, Nash AA, Dorman M. Cortical development, plasticity and re-organization in children with cochlear implants. J Commun Disord. 2009;42:272-9.
19. Evans A, Baudoin M, Knight HE, Giles A. Case report: transient auditory neuropathy with resurgence of electrophysiologic waveforms observed between the neonatal period and age 3 years. J Am Acad Audiol. 2023;34:38-44.
20. Joint Commettee in Infant Hearing. Year 2019 position statement: principles and guidelines for early hearing detection and intervention programs. J Early Hear Detect Interv. 2019;4:1-44.

Revista Médica del
Hospital General de México

PERMANYER

Check for updates

CLINICAL CASES

Dengue in pregnancy and dengue neonatal: a case report

Víctor H. Patlán-Gutiérrez[1,2], Leslie A. Vega-Pastor[1,2], Eder R. Ayala-Bailón[1,2,3], Bathsheba García-Reyes[4], and Hanna S. Gómez-Patlán[5]*

[1]Paediatric Unit, Neonatal Intensive Care Unit, Hospital General de México Dr. Eduardo Liceaga, Secretaría de Salud; [2]Department of Neonatology Unit Teaching, Faculty of Medicine, Universidad Nacional Autónoma de México. Mexico City; [3]Paediatric Unit, Hospital General de Jojutla, Jojutla, Morelos; [4]Emergency Unit, Hospital General de Pénjamo, Pénjamo, Guanajuato; [5]Department of Research, Universidad Quetzalcóatl de Irapuato, Hospital General de Irapuato, Irapuato, Guanajuato. Mexico

Abstract

We present the case of a newborn whose mother was diagnosed with dengue 3 days before the resolution of the pregnancy. At birth, the product presented data of a systemic inflammatory response, so a picture of neonatal sepsis was suspected, receiving antimicrobial treatment without finding improvement, having a torpid clinical evolution, persisting with high-grade fever and adding thrombocytopenia and lymphopenia, which is why considering the history maternal dengue diagnostic tests were performed on the product, with positive results confirming the diagnosis of neonatal dengue, initiating supportive management with a favorable evolution.

Keywords: *Neonatal dengue. Sepsis. Thrombocytopenia. High-grade fever.*

Introduction

Dengue is a disease caused by infection with one of the four variants of the dengue virus (DENV), which is transmitted by mosquitoes, mainly Aedes aegypti. It should be noted that each variant has serotype-specific immunity[1]. During pregnancy, the infection, although rare, can manifest asymptomatically or present with severe symptoms and high morbidity[2]. Transmission to the newborn can be vertical or horizontal. Vertical transmission of dengue is rare, with an estimated prevalence of 1.6-10.5%. The incubation period varies from 3 to 25 days, most commonly being 5-8 days. This transmission usually occurs in endemic areas and occurs mainly when the mother is infected during the third trimester of pregnancy. The health implications of the maternal-fetal binomial have been documented since the early 2000s[2]. It should be noted that in Mexico there are no epidemiological studies that report the exact prevalence of neonatal dengue. Machain (Mexico, 2018) conducted a study of patients from Veracruz, Tabasco, and Tamaulipas with immunoglobulin M (IgM) or NS1 for dengue positive during pregnancy in 82 patients, 31 were during the last trimester and all those that were severe occurred between gestational week 34 and 36, of these last patients, five died. Of the reported newborns, only one was low birth weight and none developed symptoms during their hospital stay[3].

The antibody response to DENV infection is primarily directed at specific serotype determinants, but there is a substantial level of serotype E cross-reactive antibodies, with the precursor membrane (pre-M) and NS1 being the main viral proteins targeted. *In vitro*, specific antibodies to the E protein can mediate infection neutralization, complement-mediated direct lysis, or antibody-dependent

***Correspondence:**
Víctor H. Patlán-Gutiérrez
E-mail: hugo_patlan@hotmail.com

Date of reception: 09-03-2024
Date of acceptance: 24-07-2024
DOI: 10.24875/HGMX.24000020

Available online: 01-04-2025
Rev Med Hosp Gen Mex. 2025;88(2):110-116
www.hospitalgeneral.mx

cellular cytotoxicity of DENV-infected cells and block the binding of the virus to cell receptors[4].

Pre-M-specific antibodies only bind to virions that have not fully matured and have remaining pre-M protein uncleaved. NS1 is not found in the virion; Thus, NS1-specific antibodies are unable to neutralize viral infection, but they can direct complement-mediated lysis of infected cells. To date, the basis for neutralization of the virus by antibodies is not well understood[4].

Clinical manifestations

It is estimated that more than 390 million DENV infections occur each year and approximately 96 million are clinically evident. Clinically apparent dengue is more common among adults, while among children, most infections are usually asymptomatic or minimally symptomatic and may occur with persistent vomiting. Clinical accumulation of fluid (ascites, pleural effusion), bleeding from the mucous membranes, lethargy or restlessness, hepatomegaly > 2 cm concurrent increase in hematocrit with a rapid decrease in platelet count. Severe plasma leak causing: shock, fluid accumulation with respiratory distress. May also present with severe bleeding[4].

It is also feasible to present severe organ involvement through aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 1000 units/L and deterioration of alertness. A primary DENV infection is defined as the first wild-type infection that an individual suffers from, while a secondary infection is the second wild-type infection caused by a different serotype of DENV. Secondary infections separated in time by more than 18 months represent the greatest risk of causing a serious clinical outcome[4].

The incubation period for DENV infection ranges from 3 to 14 days; symptoms usually develop 4-7 days after an infected mosquito bite. Phases of infection: there are three phases that can be observed in the context of a DENV infection: a febrile phase, a critical phase, and a recovery phase; however, the critical phase is not observed in all infection categories[4].

Within the 1997 WHO classification scheme, the three phases of infection occur in the context of dengue hemorrhagic fever and dengue shock syndrome; dengue fever (DF) includes febrile and recovery phases, but no critical phases. Within the WHO's 2009 classification scheme, the three phases of infection occur in the context of severe dengue and dengue with warning signs; dengue without warning signs includes febrile and recovery phases, but no critical phases[5].

Febrile phase: the febrile phase of DENV infection is characterized by sudden onset high fever (≥ 38.5°C) accompanied by headache, vomiting, myalgia, arthralgia, and transient macular rash in some cases. Children have a high fever but are usually less symptomatic than adults during the febrile phase. The febrile phase lasts 3-7 days, after which most patients recover without complications. Headache, eye pain (i.e., pain with eye movement), and joint pain occur in 60-70% of cases. The rash occurs in about half of the cases, being more common during the primary infection than during the secondary infection. When present, the rash usually occurs 2-5 days after the onset of fever[6-8].

In children, clinically significant bleeding rarely occurs, usually associated with prolonged, deep shock. It should be noted that there is not always significant thrombocytopenia when hemorrhagic manifestations occur and when it is present, the risk of bleeding increases. Physical examination may demonstrate conjunctival injection, pharyngeal erythema, lymphadenopathy, and hepatomegaly. Facial edema, petechiae (on the skin and/or palate), and bruising (particularly at venipuncture sites) may be observed[9,10].

A biphasic ("saddle") fever curve has been described in about 5% of cases; in these patients, acute febrile illness remits and then recurs about a day or two later; the second febrile phase lasts 1 or 2 days. Leukopenia and thrombocytopenia (≤ 100,000 cells/mm) are common[11,12] (Fig. 1). Serum aspartate transaminase (AST) concentrations are usually elevated and these elevations are usually moderate (2-5 times the upper limit of normal), but marked elevations (5-15 times the upper limit of normal) occasionally occur. Elevated liver enzymes are common in the febrile phase; synthetic liver dysfunction (i.e., elevated activated partial thromboplastin time) and fibrinogen decreases are not frequently identified.

Between days 3 and 7 of the disease, significant vascular leakage reduces intravascular volume and decreases organ perfusion. Corresponding clinical manifestations may include persistent vomiting, increasingly severe abdominal pain, painful hepatomegaly, development of pleural effusions and/or ascites, mucosal hemorrhage, and lethargy or restlessness; laboratory findings may include a high or increasing hematocrit level (≥ 20% from baseline) concurrent with a rapid decrease in platelet count[13-16] (Fig. 1).

Critical phase: The vast majority of infections that progress to a critical phase are the result of second DENV infections that occur more than 18 months after a first resolved infection. However, a subset of critical infections

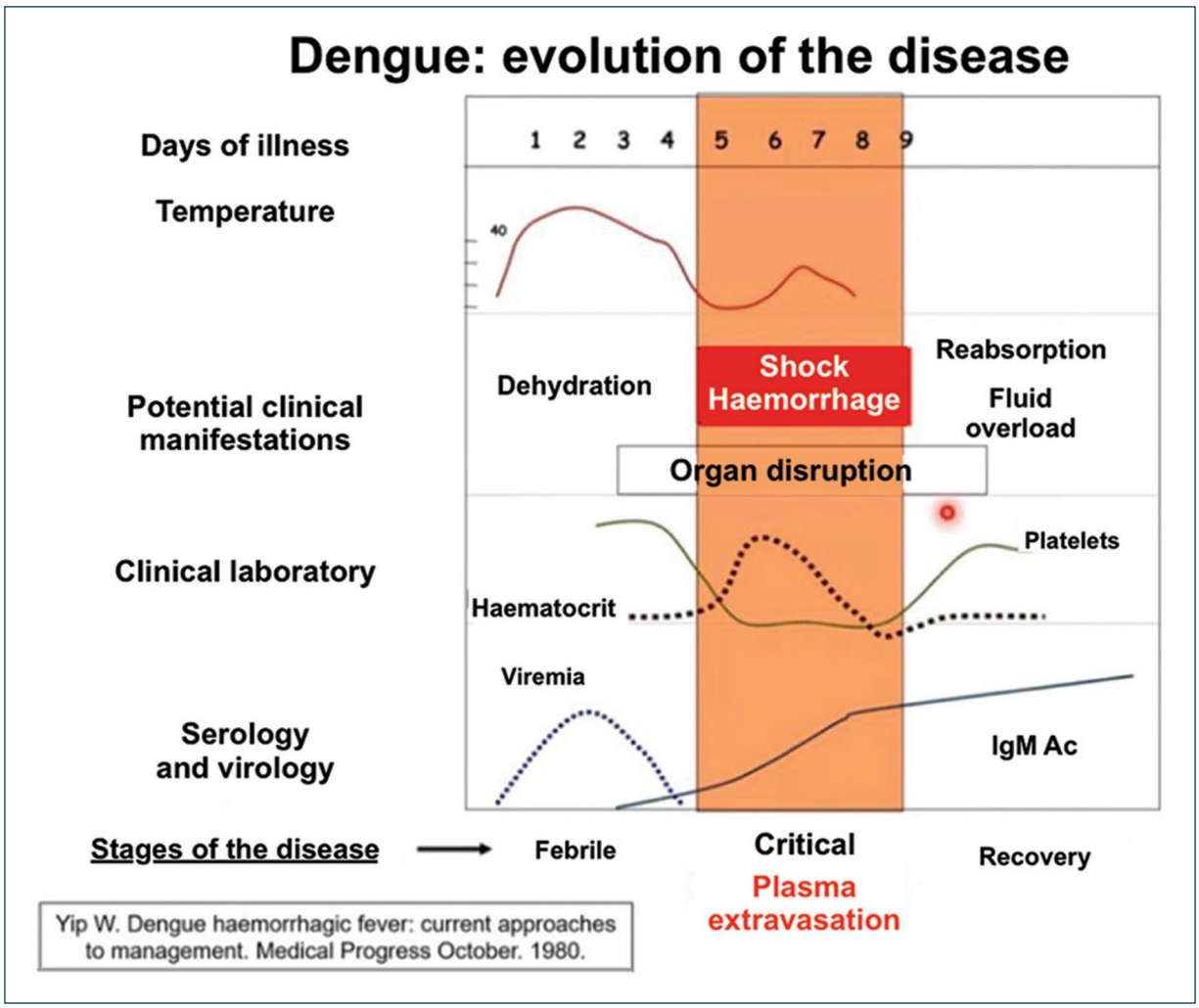


Figure 1. The image shows the natural evolution of the disease where first there is a febrile phase that lasts approximately 5 days and then presents changes in the blood count where the progressive decrease of the platelet count stands out, this being the critical stage of the disease.

occurs in children under 1 year of age, at the time when maternal antibodies are below protective levels and the child experiences a primary wild-type infection. The critical phase lasts 24-48 h. Initially, adequate circulation can be maintained by physiological compensation, resulting in a narrowing of pulse pressure (systolic pressure minus diastolic pressure ≤ 20 mmHg). In confirmed cases of dengue in the mother, most newborns do not show symptoms, but they may present with neonatal sepsis and present with fever, rash, irritability, and bleeding[17].

Presentation of the case

This is a full-term male newborn, son of a 21 year old woman, G1, P0, C1, A0. The mother received antenatal care at her local health center, with a total of 8 consultations, and underwent 3 reported ultrasounds with no obvious abnormalities. In addition, TdPA immunizations were administered during pregnancy, although immunization against influenza and COVID-19 was denied by the patient.

During pregnancy, the patient denied having presented threats of abortion, threat of pre-term delivery, pre-eclampsia, gestational diabetes, or other complications of pregnancy. She developed a urinary tract infection at 32 weeks of gestation, receiving unspecified antimicrobial treatment and finding improvement in symptoms. In addition, he presented cervicovaginitis on two occasions, which were managed with unspecified antimicrobial treatment with improvement of symptoms. Three days before the resolution of the pregnancy, the patient experienced headache, photophobia, myalgias,

Table 1. The values reported in the serial blood counts show the natural evolution of the disease where after the febrile stage a progressive decrease in platelet and leukocyte count begins, with an increase in hematocrit and an improvement in platelet count as well as in leukocytes from day 7 of the disease

Days of life	Platelets × 10^3	Hemoglobin (g/dL)	Hematocrit (%)	Leukocytes × 10^3	Neutrophils × 10^3	Lymphocytes × 10^3	Monocytes × 10^3	Eosinophils × 10^3
1	222	12.7	39.30	15100	8170	5770	920	180
5	32	14.9	46.50	1500	450	450	390	40
6	16	14.6	43.4	3900	1310	1950	530	80
7	130	11.8	36.10	11800	3000	6930	1560	220

arthralgias, and unquantified fever. She self-medicated with paracetamol, without finding improvement. 24 h after the onset of symptoms, they decide to go for evaluation at their health center, where dengue is probably diagnosed, given the typical manifestations and its location in an endemic area of Morelos. The patient was admitted to the General Hospital of Jojutla where she was kept under surveillance and laboratory studies were taken which reported: Leukopenia (4 thousand) and a decrease in platelets (150 thousand, previously 180 thousand) for which a polymerase chain reaction (PCR) test was performed for the detection of dengue. Given the clinical suspicion of the diagnosis and maternal complications, it was decided to terminate the pregnancy by cesarean section.

A male product of 40 SDG per Capurro was obtained through the abdomen, who cried and breathed at birth presenting a weak cry and a heart rate > 100 beats/min, with a report of meconium-stained fluid. The product had a weight of 3700 g height: 52 cm APGAR: 8/8, at 10 min of life the product presents data of respiratory distress at the expense of: discrete intercostal retraction, discrete nasal flaring, and respiratory whine receiving a Silverman score of 3, so it was decided to transfer him to the neonatal intensive care unit (NICU) where a chest X-ray was taken, which showed evidence of horizontal costal arches and an increase in intercostal spaces, in addition to a predominant nodular infiltrate in the right lung. An umbilical catheter was placed in an intrahepatic position and laboratory studies were taken, identifying in the blood count a hemoglobin of 12.7 g/dL, a hematocrit of 39.3%, a leukocyte count of 15.1 (94.1% neutrophils, 38.2% lymphocytes, 6.1% monocytes, 1.2% eosinophils, 0.4% basophils) and platelets of 222 thousand. Cord blood gases reported: a pH of 7.3, PCO_2 of 47 mm Hg, pO_2 of 10 mm Hg, lactate of 2.6 mmol/L, DB - 3.3 mmol/L, and HCO_3 of 23.1 mmol/L.

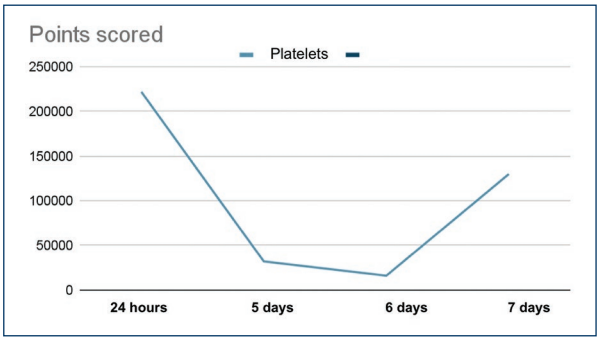


Figure 2. The graph shows a downward curve of the platelet count in the newborn during the course of the disease in which a clear decrease in the platelet count can be seen that becomes more pronounced between days 5 and 6 of the disease with a significant increase in the platelet count from day 7 of the disease evidencing the recovery stage.

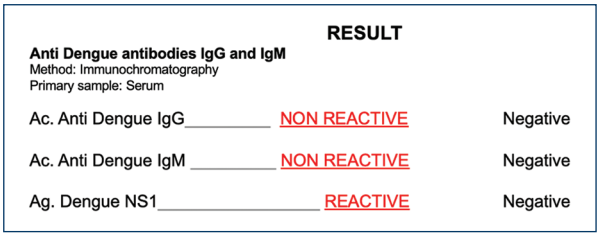


Figure 3. The report of the diagnostic test performed on the newborn whose result was positive for dengue when Ag. NS1 was positive and is shown. NS1 is one of the 7 non-structural proteins of the dengue virus that are thought to be involved in viral replication, so a positive result for NS1, with negative immunoglobulin M (IgM) and IgG indicates recent infection, probably with a disease time of < 5 days.

The product was admitted to the NICU with the diagnosis of "full-term newborn (40 weeks of gestation) with high weight for gestational age, meconium aspiration

syndrome and child of a mother with dengue without alarm data". Antimicrobial treatment with ampicillin and amikacin was initiated due to meconium aspiration and the patient was kept fasting receiving supplemental oxygen through nasal CPAP due to the persistence of respiratory distress that did not improve with supplemental oxygen supply through nasal tips.

At 24 h of life, nasal CPAP was removed and nasal prongs were progressed due to improvement of the ventilatory pattern, presenting adequate tolerance, and PCR test results for dengue were collected from the mother, which reported positive NS1 with DENV-3 serotype. The product presented adequate clinical evolution, however, on the 5th day of life the newborn presented a fever quantified up to 39°C, so new blood biometry was taken that reported: hemoglobin of 14.9 g/dL, a hematocrit of 46.5%, a leukocyte count of 1500, (29.9% neutrophils, 29.9% lymphocytes, 26% monocytes, 2.4% eosinophils, 11.8% basophils, platelets of 32 thousand and liver function tests that reported ALT/TGP: 38.0 U/L, serum albumin: 3.10 g/dL evidencing a decrease in platelet count (Table 1) so it was decided to perform a specific PCR test for dengue and water support was started at 110 mL/kg/day with dynamic management of intravenous fluids and thermal control with paracetamol and starting management with vitamin K. The patient continued to be feverish, irritable, but remained without bleeding data. 24 h later, new control laboratory studies were taken which reported hemoglobin of 14.6 g/dL, a hematocrit of 43.4%, a leukocyte count of 3900, (33.7% neutrophils, 50.1% lymphocytes, 13.5% monocytes, 2.1% eosinophils, 0.6% basophils,) platelets of 16 thousand (Fig. 2). TP: 14.62, APTT: 64.09, INR: 1.09, so it was decided to transfuse platelets and fresh plasma, on the 7th day of life the PCR report for dengue was collected, identifying reactive Ag. NS1 confirming the infection in the neonate (Fig. 3).

Discussion

This clinical case presents a complex scenario in which maternal dengue during pregnancy conditions complications in the pregnant woman, causing the resolution of the pregnancy urgently through the abdominal route, associating neonatal complications, in particular a meconium aspiration syndrome and a clinical picture that initially suggested neonatal sepsis. Although the diagnosis of dengue in the mother was clinical, the clinical picture of the newborn was larval in the first hours of life, representing a real challenge for the diagnosis since, as previously described, vertical transmission is rare, once the newborn began with a picture of persistent high-grade fever, complementary laboratory studies were repeated, evidencing the development of thrombocytopenia In addition, it was possible to collect the result of the confirmatory tests for dengue carried out on the mother, which yielded a positive result, so diagnostic tests were carried out on the newborn, thus confirming the diagnosis. Another of the challenges identified in this clinical condition was the adequate water management of the newborn since, as described, there is no evidence or guidelines that guide the most appropriate water management in these patients, having opted in this case to carry out a dynamic water management similar to that of any other newborn, carrying out fluid increases of 12.5 mL/kg/day every 24 h maintaining strict control of water balance and diuresis, another challenge during the course of the disease in the newborn was the risk of developing bleeding data, so it was decided to initiate management with Vitamin K and once a thrombocytopenia of 16,000 was identified, it was decided to transfuse platelets. A transfontanelar ultrasound was performed where hemorrhage at this level was ruled out. It should be noted that at no time was there any data of bleeding at another level. Temperature management was carried out with alternating paracetamol and metamizole, thus achieving adequate thermal control.

The relationship between maternal dengue infection and the risk of meconium aspiration syndrome in the newborn is a question that requires further investigation. Dengue is a mosquito-borne disease that affects people of all ages, but the focus on neonatal dengue is focused on newborns who acquire the virus during birth or shortly after birth. Although neonatal dengue is rare, it is important to understand its clinical characteristics, diagnosis, and management to ensure adequate care and prevent complications, it should be noted that the management of the patient with dengue involves a high intake of fluids which, so far, has not been fully studied in the newborn, making it a real challenge for the treating physician.

Clinical characteristics in the newborn

Neonatal dengue presents variably and can be asymptomatic or have symptoms ranging from mild to severe. Typical symptoms of dengue in neonates may include:

- Fever may be one of the first signs of infection in neonates, although body temperature may not rise significantly. Irritability and inconsolable crying.
- Poor diet or difficulty sucking, vomiting and diarrhea, respiratory symptoms, hemorrhagic manifestations:

thrombocytopenia and hemorrhagic manifestations, such as petechiae, bleeding gums, or nose, can occur in severe cases.

Diagnosis

Diagnosing neonatal dengue can be challenging due to the variety of symptoms that can be mistaken for other neonatal conditions. Diagnosis is based on a combination of clinical criteria and laboratory tests.

In cases of confirmed maternal dengue, delivery care is carried out under usual conditions, but precautions are taken to avoid contamination by blood and fluids. A series of diagnostic tests and evaluations are performed on both the newborn and the mother.

Diagnostic tests and evaluations

1. Confirmation of the diagnosis in the newborn: a PCR for dengue and specific IgM for dengue of cord blood or the newborn is requested in the first 48 h of life. IgM dosing for dengue may need to be repeated later, as its titers may not be detected initially.
2. Clinical evaluation: a complete blood count with lamina, C-reactive protein, procalcitonin, and blood culture is performed after 6 h of life.
3. Attention to warning signs: thrombocytopenia of < 100,000 and an increase in hematocrit of 20% are considered as warning signs. Leukopenia may also be observed, indicating severity in this age group[17].

Hospitalization of the newborn

- The hospitalization sector is adapted according to the clinical situation, guaranteeing isolation, control, and strict and permanent monitoring.
- Even if there are no clinical manifestations, the patient is admitted to an area that ensures isolation, with constant monitoring. In asymptomatic cases, it is not necessary to separate the newborn from the mother, as long as the clinic allows it and adequate controls are maintained in the co-housing.
- Vector isolation with mosquito nets and tulle is implemented, ensuring that there are no vectors (mosquitoes) in the area before patient admission.

Treatment

- Treatment is adjusted to the clinical situation of the newborn.
- In asymptomatic cases, the risk and benefit of initiating breastfeeding are evaluated, considering that some authors suggest the possibility of transmission of the disease through milk.
- In situations of shock, the protocol for the treatment of shock in the neonatal period is followed. Volume replacement is adapted to the clinical situation, starting with a physiological solution at 10 mL/kg of weight in 30 min to 1 h. Sudden changes in osmolarity and flow due to the high risk of intracranial bleeding are avoided.

Evolution and discharge

If the newborn with dengue remains separated from his mother and is asymptomatic in the first 7 days, control and follow-up can continue in mother-child accommodation, maintaining the aforementioned isolation measures.

- The initiation of breastfeeding is allowed according to the evolution of the maternal disease.
- After 15 days, the patient is discharged home with home monitoring by the health team[17].

Management of neonatal dengue focuses on supporting and treating symptoms. Measures may include:

- Hydration: maintaining hydration is crucial, especially if the newborn has a fever and vomiting. Intravenous fluids may be needed in severe cases.
- Fever management: safe and suitable antipyretics for the neonate can be used to control fever.
- Platelet transfusions: in cases of severe thrombocytopenia or bleeding manifestations, transfusions of platelets and other blood products may be given as needed.

Prognosis

The prognosis of neonatal dengue varies depending on the severity of the infection and how quickly treatment is started. In general, most neonates recover completely with proper management. However, in severe cases, neonatal dengue can be life-threatening, underscoring the importance of medical care.

Transmission mechanism

Vertical transmission of dengue can occur in several ways:

- Intrauterine: during pregnancy, the DENV can cross the placenta and reach the fetus. This route of infection can occur at any stage of pregnancy, although it

is generally considered uncommon. During delivery: If the mother has dengue and gives birth to a baby, there is a chance that the newborn may become infected during delivery, especially if the baby comes into contact with blood or maternal body fluids contaminated with the virus.

- Breastfeeding: although transmission of dengue through breast milk is rare, the virus has been documented to be excreted in breast milk. This raises the possibility that a newborn may become infected if fed breast milk from a mother with active dengue. However, breastfeeding is not considered a common route of infection for neonatal dengue[17].

Clinical manifestations of neonatal dengue transmitted vertically:

- The diagnosis of vertically transmitted neonatal dengue is based on a combination of clinical criteria and laboratory tests, such as PCR or reverse transcription-PCR tests to detect dengue viral RNA in newborn blood samples and serological tests to detect IgM and IgG antibodies. The management of vertically transmitted neonatal dengue is similar to that of acquired neonatal dengue after birth. It focuses on symptom support and treatment, including hydration, fever care, and monitoring for bleeding manifestations. In severe cases, transfusions of platelets and other blood products may be necessary[17].

Conclusion

Mother-to-child transmission of dengue is a rare but important route of infection. Neonatal top-down dengue can present with a variety of symptoms, and its diagnosis and management require careful clinical evaluation and laboratory testing.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from patients, and received approval from the Ethics Committee. The SAGER guidelines were followed according to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

References

1. Organización Panamericana de la Salud. Guías Para la Atención de Enfermos en la Región de las Américas. 2nd ed. Available from: https://iris.paho.org/bitstream/handle/10665.2/28232/9789275318904_esp.pdf?sequence=1&isallowed=y [Last accessed on 2024 Mar 14].
2. Juárez-Campos CE, Duran-Guerra D, Ceja-Mejía ÓE, Cortez-Comparan D, Baeza-Casillas JA, Díaz Santana-Bustamante DE, et al. Dengue neonatal: serie de casos. Rev Latin Infect Pediátr. 2022;35:81-5.
3. MacHain-Williams C, Raga E, Baak-Baak CM, Kiem S, Blitvich BJ, Ramos C. Maternal, fetal, and neonatal outcomes in pregnant dengue patients in Mexico. Biomed Res Int. 2018;2018:9643083.
4. Thomas SJ, Rothman AL. Infección por el virus del dengue: patogenia. Infectio. 2023;29:4-5.
5. Organización Mundial de la Salud. Dengue: Directrices para el Diagnóstico, Tratamiento, Prevención y Control. Nueva ed. Ginebra: OMS: 2009. Available from: https://www.who.int.pbidi.unam.mx:8/080/tdr/publications/documents/dengue-diagnosis.pdf?ua=1 [Last accessed on 2016 Dec 07].
6. Fukusumi M, Arashiro T, Arima Y, Matsui T, Shimada T, Kinoshita H, et al. Dengue sentinel traveler surveillance: monthly and yearly notification trends among Japanese travelers, 2006-2014. PLoS Negl Trop Dis. 2016;10:e0004924.
7. Trofa AF, DeFraites RF, Smoak BL, Kanesa-Thasan N, King AD, Burrous JM, et al. Dengue fever in US military personnel in Haiti. JAMA. 1997;277:1546-8.
8. Leder K, Torresi J, Brownstein JS, Wilson ME, Keystone JS, Barnett E, et al. Travel-associated illness trends and clusters 2000-2010. Emerg Infect Dis. 2013;19:1049-73.
9. Diaz A, Kourí G, Guzmán MG, Lobaina L, Bravo J, Aroldo R, et al. Cuadro clinico de la fiebre hemorragica del dengue/sindrome de choque del dengue en el adulto. Bol Oficina Saint Panam. 1988;6:560-71.
10. Guzmán MG, Kourí G, Martínez E, Bravo J, Riverón R, Soler M, et al. Clinical and serologic study of Cuban children with dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). Bull Pan Am Health Organ. 1987;21:270-9.
11. Díaz FA, Martínez RA, Villar LA. Criterios clínicos para diagnosticar el dengue en los primeros días de enfermedad. Biomédica. 2022;26:22-30.
12. Potts JA, Rothman AL. Clinical and laboratory features that distinguish dengue from other febrile illnesses in endemic populations. Trop Med Int Health. 2008;13:1328-40.
13. Halstead SB. Dengue. Lancet. 2007;370(9599):1644-52.
14. Tanner L, Schreiber M, Low JG, Ong A, Tolfvenstam T, Lai YL, et al. Decision tree algorithms predict the diagnosis and outcome of dengue fever in the early phase of illness. PLoS Negl Trop Dis. 2008;2:e196.
15. Moraes M, Mayans E, Sobrero H, Borbonet D. Dengue en el recién nacido. Arch Pediatr Urug. 2016;87:269-71.
16. Brítez S, Mir R, Lacarrubba J, Mendieta E, Céspedes E, Genes L. Dengue de transmisión vertical: revisión de una serie de casos. Pediatría (Asunción). 2014;41:25-31.
17. García-Rivera E, Rigau-Pérez J. Dengue virus. In: Hutto C, editor. Infectious Disease: Congenital and Perinatal Infections, A Concise Guide to Diagnosis. Totowa, NJ: Humana Press Inc.; 2006. p. 187-98.