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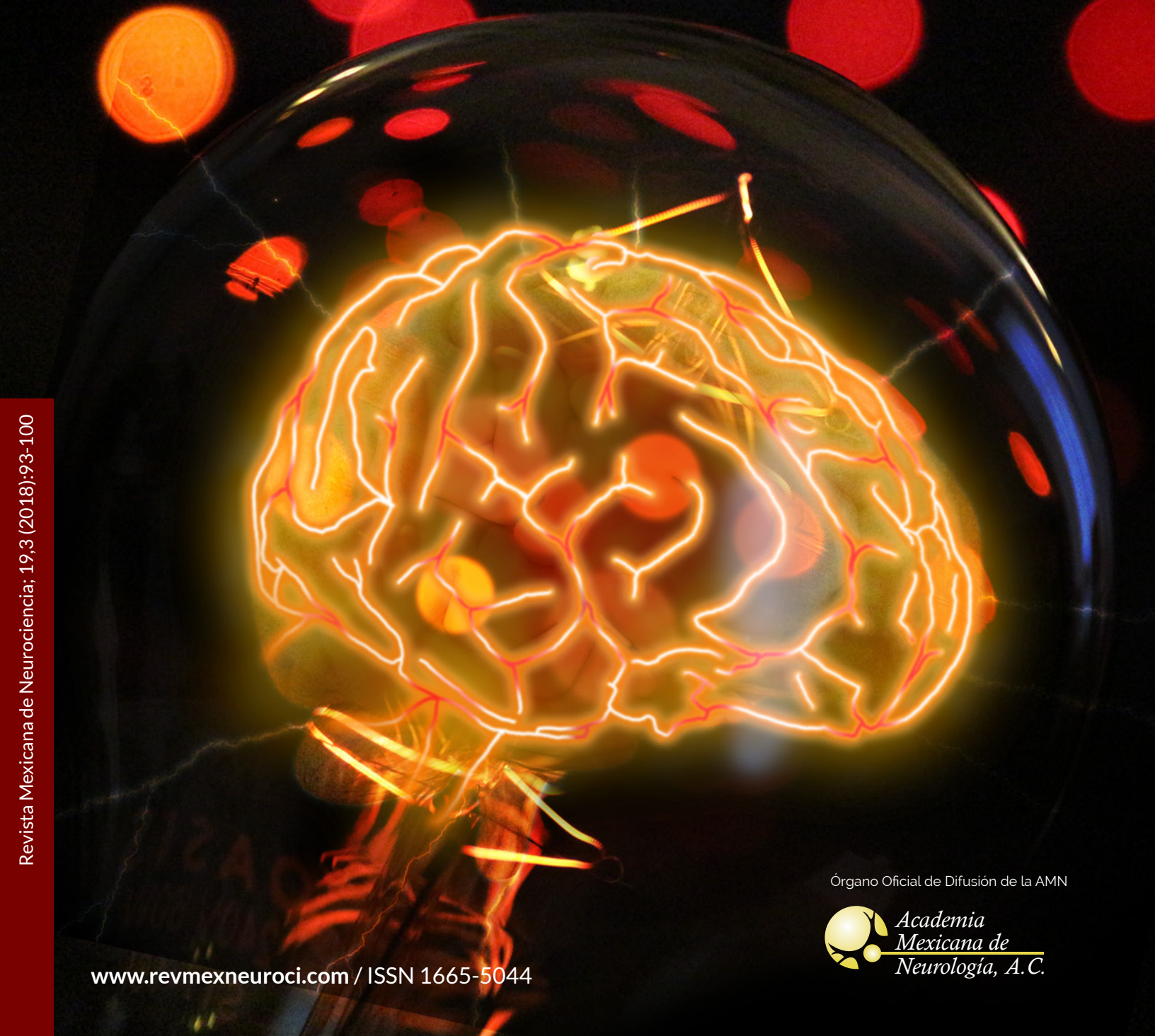

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Case report

Jaime Iván Castro-Macías,[1] Gabriel Santos-Vázquez,[2] Marcos Oswaldo Díaz-Campos,[2] Iván Quijas-Aldana,[2] Ricardo García-Cázarez.[1]

[1]*Neurosciences Service, High Specialty Regional Hospital of Bajío, León, Gto. México.*
[2]*Department of Medicine and Nutrition, University of Guanajuato, León, Gto. México.*

Amyotrophic Lateral Sclerosis during pregnancy: an uncommon association

Esclerosis Lateral Amiotrófica y Embarazo: una asociación poco común

Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that shows a combination of upper and lower motor neurons signs and symptoms. The association of ALS and pregnancy has low prevalence due to demographic characteristics of the disease.

Case: A 29-year-old woman, healthy, who comes to the clinic at week 29 of gestation, manifests progressive weakness, distal hypotrophy, and dysphagia. On examination signs of upper and lower motor neuron with involvement in cervical, bulbar, thoracic and lumbar segments. The pregnancy developed without complications; adequate prenatal control, and cesarean section as resolution of pregnancy.

Conclusion: Pregnancy may be associated with the development of latent ALS due to hormonal factors related to the increase of progestogens, which would decrease the neuroprotective effect of estrogens, being the trigger of the disease. Vaginal delivery is facilitated, but respiratory compromise would determine the cesarean delivery.

Keywords

Amyotrophic lateral sclerosis, pregnancy, motor neuron disease, neurodegeneration.

Resumen

Introducción: La esclerosis lateral amiotrófica (ELA) es una enfermedad neurodegenerativa progresiva, con afección de las neuronas motoras superior e inferior, caracterizada por debilidad, atrofia y fasciculaciones. La asociación de ELA y embarazo tiene baja prevalencia debido a las características demográficas de la enfermedad.

Caso clínico: Mujer de 29 años, sana, la cual acude a consulta en la semana 29 de gestación manifestando debilidad progresiva, hipotrofia distal y disfagia. A la exploración signos de afección de motoneurona superior e inferior en segmentos cervical, bulbar, torácico y lumbar. El embarazo se desarrolló sin complicaciones; control prenatal adecuado, y resolución del embarazo por cesárea.

Conclusión: El embarazo podría estar asociado al desarrollo de una ELA latente debido a factores hormonales relacionados al aumento de los progestágenos, los cuales disminuirían el efecto neuroprotector de los estrógenos, siendo el gatillo de la enfermedad. El parto vaginal se ve facilitado, pero el compromiso respiratorio determinaría la vía cesárea.

Palabras clave

Esclerosis lateral amiotrófica, embarazo, enfermedad de neurona motora, neurodegeneración.

Corresponding author:
Dr. Jaime Iván Castro Macías
Servicio de Neurociencias, Hospital Regional de Alta Especialidad del Bajío, León, Gto. México. Boulevard Milenio 130, San Carlos la Roncha, 37660 León, Guanajuato.
Phone: +52 477 267 2000
E-mail: JICM772003@yahoo.com.mx

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease characterized by progressive loss of upper and lower motor neurons manifested by progressive weakness, atrophy, spasticity, fasciculations, and abnormal reflexes with a survival of three to five years after diagnosis.[1] The incidence is higher in men with a 1.2-1.5:1 ratio. The age of onset is usually between the fifth and sixth decade of life.[1,2] ALS during pregnancy is uncommon, only 18 cases have been described worldwide.[3-13] The largest series of cases with this association was described on the island of Guam in 1956 with a higher prevalence of the familial variant of the disease.[6,15] In Mexico, there are two cases reported.[14] We describe a case in this article.

Case report

Female, twenty-nine years old, right-handed, primiparous, with no family history of neuromuscular diseases, drug use, or toxic exposure had pregestational diabetes documented at week 14. At week 29, she sought assessment due to asymmetric weakness predominantly in the upper extremities. Onset of symptoms was one month prior to the diagnosis of pregnancy. The lower extremities were involved three months later. She also presented dysphagia and spastic dysarthria. The physical examination found a globose abdomen with a single live product in cephalic presentation and a fetal heart rate of 140 beats per minute. The neurological exploration found spastic dysarthria, dysphagia, and Vernet's syndrome effects. Muscular strength was 3/5 proximal and 4/5 distal in upper extremities, and 4/5 proximal and distal in lower extremities on the Medical Research Council (MRC) grading system. Additionally, there was generalized atrophy of distal predominance (Aran-Duchenne hands), spasticity, generalized hyperreflexia, extensor plantar response (Babinski), Hoffmann, and bilateral Trömner. Basic laboratory studies, thyroid profile, cytochemical, cytological analysis, and cerebrospinal fluid (CSF) cultures were normal. VDRL (Venereal Disease Research Laboratory), ELISA (Enzyme-Linked Immunosorbent Assay) and HIV (Human Immunodeficiency Virus) were negative. Antiganglioside antibodies (GM1) were not found. Magnetic resonance imaging (MRI) of the brain and spinal cord were normal. Electromyography (EMG) showed a neuronal-neuropathic pattern with acute and chronic denervation, as well as indirect affection of the upper motor neuron by F-wave facilitation. These findings support the diagnosis of defined ALS, according to the revised criteria of El Escorial and Airlie House, with neurophysiological support in the Awajishima criteria.[16] Resolution of the pregnancy was via cesarean section, using regional anesthesia, obtaining one single live product. The evolution of the patient during the puerperium was torpid due to respiratory compromise 30 days after the obstetric event, warranting advanced management of the airway, nevertheless presenting cardiorespiratory arrest and death. The development of the product had a normal evolution from birth until the first six months of postnatal follow-up.

Discussion

Despite the low prevalence, hormonal factors have an impact on the incidence, as well as on the evolution of the disease. Estrogens have a neuroprotective effect, not only in ALS, but also in Alzheimer and Parkinson.[3] The possible mechanisms of neuroprotection of these hormones are related to the potentiation of the release of neurotrophins, as well as the interaction with various neurotransmitters.[17] Recently, the molecular pathways of estrogen-mediated neuroprotection have been described through inactivation of the NADPH-oxidase complex and reduction of oxidative damage in motoneurons.[18] Despite this, it has been observed that the effects of estrogen are contrasting regarding its neuroprotective qualities. In a group of postmenopausal women

who received hormone replacement therapy, early signs of the disease were documented without an impact on the onset and progression of symptoms related to ALS.[17] The proposed theory regarding this failure in neuroprotection is attributed to the fact that receptors for estrogens are located in the dorsal horn of the spinal cord, while the androgen receptors are located in its motor neurons.[17] However, exposure to exogenous estrogens and progestogens, due to the use of combined hormonal contraceptives and hormone replacement therapy, decreases the risk of developing ALS.[19]

It has also been observed that every extra year of the reproductive period in women, due to the greater exposure of endogenous estrogens, decreases the risk of developing ALS, increasing survival.[20] In in vitro studies, estrogen pretreatment protected cortical neurons from glutamate toxicity.21 In transgenic mice, carriers of the mutation in the SOD-1 gene which were ovariectomized, there was an accelerated progression of the disease and a decrease in survival. In another group of ovariectomized mice treated with 17 β-estradiol, the progression of the disease decreased significantly.[22]

It is important to consider the high levels of progesterone during pregnancy, since it was observed in in vitro studies that this hormone decreases the expression of the estrogen receptor in neuronal cultures, decreasing therefore the neuroprotective effects of estrogen regardless of its concentration.[23] However, in nonpregnant women, endogenous progesterone levels have been shown to be correlated with a better prognosis and survival of patients with ALS, since they have a neuroprotective and promyelinating effect.[24] The proposed mechanism is due to activation of autophagy in cortical astrocytes. In murine models the autophagy induced by progesterone in the medullary neurons protects them from the neurodegeneration induced by the mutation in the gene G93A-SOD1.[25]

The relatively higher concentrations of progesterone with respect to estrogen during pregnancy could be related to the mechanisms previously proposed to trigger ALS during pregnancy, since in more developed models it has been described that the molecular pathways of neuroprotection in this disease are mediated mainly by estrogens.[18]

In addition to the potential hormonal effect, the activation of cytokines and neuroinflammation mediated by other routes may increase the susceptibility to develop ALS during pregnancy, since, during this state, there is an increase in the concentration of cytokines that have a toxic effect on motor neurons in susceptible patients.[26] These neurons can degenerate if they also have mutations in the SOD-1 gene or other neuroprotective molecules such as vascular endothelial growth factor (VEGF), since polymorphisms in the gene of this molecule are related to the development of ALS during pregnancy.[27] Based on these findings, it could be speculated that pregnancy could act as a trigger for a preexisting but clinically silent ALS in genetically susceptible patients, in addition to epigenetic factors involved.[28,29]

Phenotypic differences have been reported: spinal variants predominate in men, while bulbar variants predominate in women.[30] One possible explanation is due to the vulnerability of the bulbar cranial nerves related to the increase in the expression of the receptor for N-methyl-D-aspartate (NMDA), which is promoted by estrogenic activity, which favors glutamate toxicity.[31]

During pregnancy, there is a physiological increase in ventilatory requirements of 40% because pregnancy causes a deterioration of respiratory function related to uterine growth.4 Therefore, in patients with this association, ventilatory support is required during the gestational period and delivery,[12] especially in advanced cases of the disease, since there is a limitation in the respiratory reserve with respect to diaphragmatic function.[4]

The treatment during advanced stages represents a serious problem. Bulbar involvement, in addition to affecting respiration, affects swallowing and this is additional to the physiological hypermetabolism inducing malnutrition and cachexia in final stages.[4]

Treatment with riluzole is considered class C during pregnancy due to teratogenic effects reported in animal tests; however, the risk in humans has not been evaluated in appropriate clinical studies. There is a report of a woman with ALS during pregnancy who received this treatment without deleterious effects on the product.[32]

Regional anesthesia offers advantages over general anesthesia, since it reduces pain intensity, while preserving bulbar function.[10]

There is no consensus regarding the resolution of pregnancy via vaginal birth or cesarean section. Because the uterine musculature is not affected, but the pelvic floor is, which lacks tone, this could facilitate vaginal delivery. Since the sensitivity is preserved in ALS, the patient would have no difficulty perceiving uterine contractions.[32] Bulbar compromise, as well as of the respiratory musculature, would determine the resolution of pregnancy via cesarean section.[3,15]

Regarding the association of ALS and pregnancy, the frequency of congenital malformations has only been reported in two cases: anencephaly and cleft palate. It has not been determined, however, if they have a direct relationship with ALS.[6,15]

Conclusion

The association of ALS and pregnancy is uncommon, but the diagnostic suspicion is important. Data of upper and lower motor neuron involvement should be taken into account since it impacts the gestational care of the mother and the product, as well as the resolution of the pregnancy.

Conflicts of interest

The authors state that there are no relevant conflicts of interest in this study.

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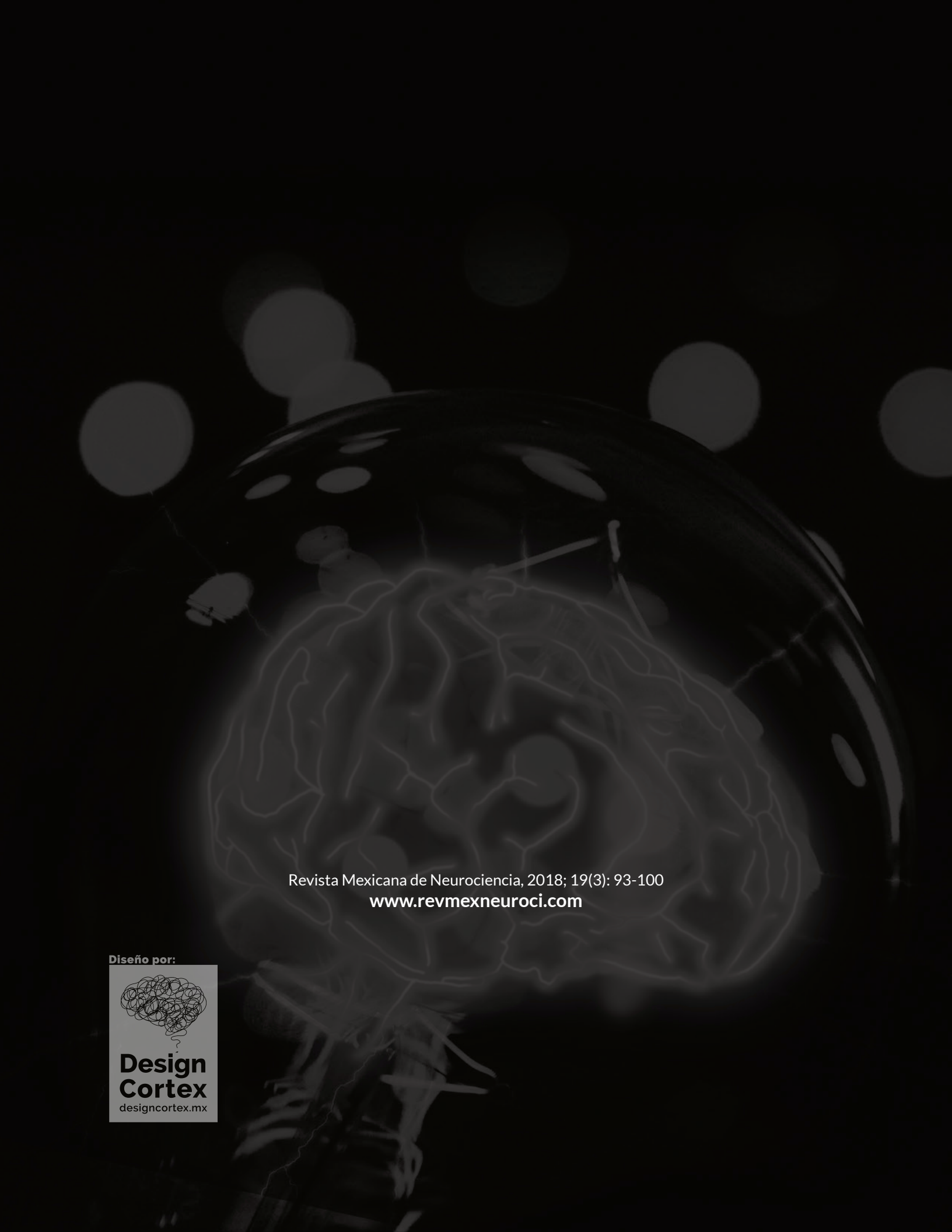

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