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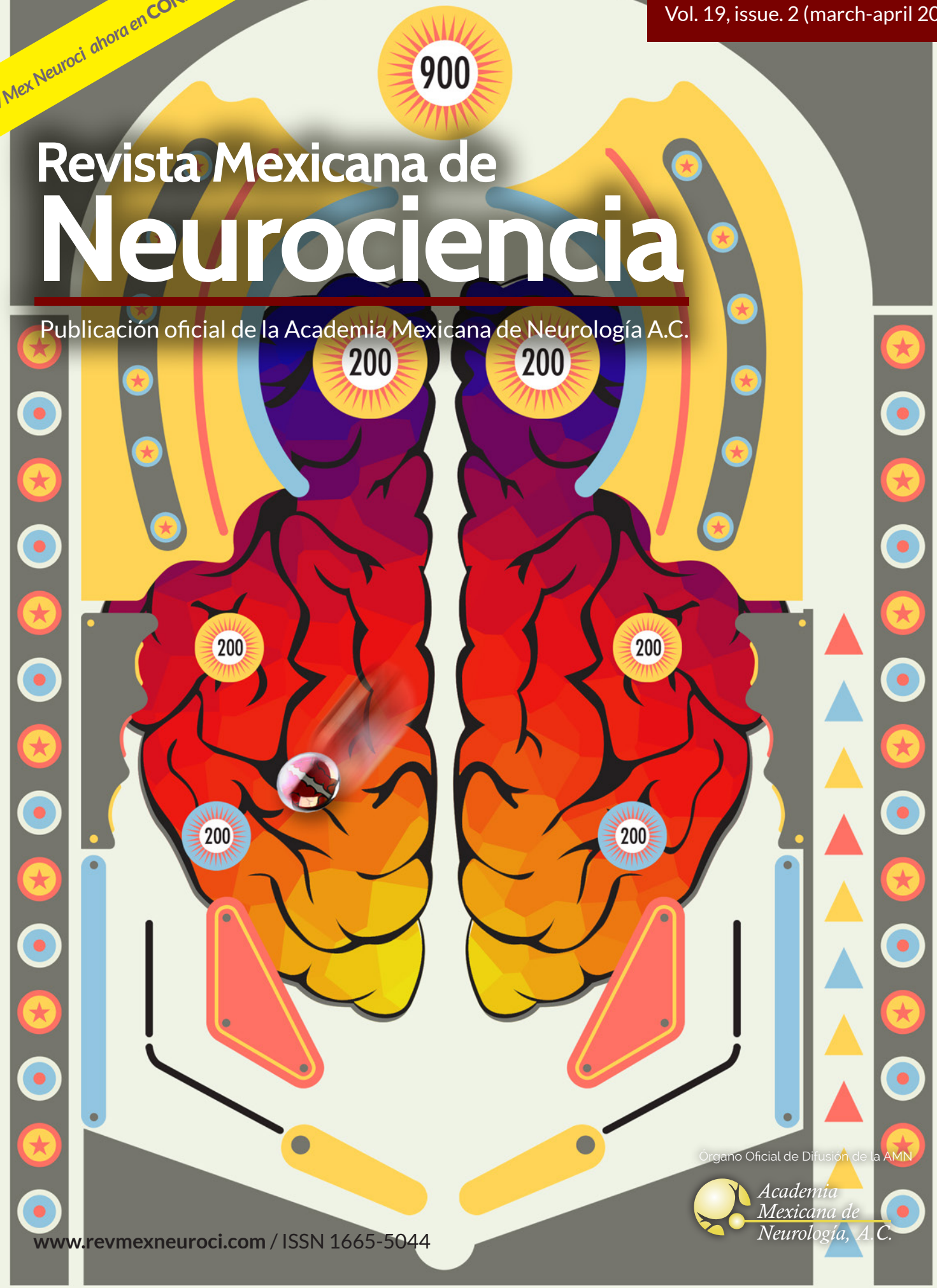

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Original contribution

Fabry disease. Report of twelve cases

Enfermedad de Fabry. Reporte de doce casos

Sofía Lucila Rodríguez-Rivera,[1] Martín Arturo Silva-Ramírez,[1] María Castro-Tarín,[1] Flora López-Cebada.[1]

[1]*Department of Pediatric Neurology, La Raza National Medical Center. Mexico City, Mexico.*

Abstract

Introduction: Fabry disease is one of the lysosomal storage diseases caused by deficiency of the enzyme alpha galactosidase acid. In childhood and adolescence, paroxysmal pain and acroparesthesias are characteristic.

Objective: Report clinical characteristics, pain scale, level of IQ and quality of life in children with Fabry disease.

Methods: The most frequent neurological manifestations were determined by clinical history and neurological examination of children with Fabry Disease receiving enzyme replacement therapy at the HG CMN La Raza, from January to May 2016. Brief Pain Inventory,[4] quality of life SF366 survey and Wechsler's scale of intelligence for children reviewed (WISC-R) Verbal Scale[5] were applied.

Results: We included 12 patients. Female gender (67%). Onset of neurological manifestations: male 6.25 years old and female 9.12 years old. Autonomic and sensitive neuropathy were the most frequent neurological manifestations. Nine patients presented neuropathic pain (75%), with pain improvement after treatment as reported by the parents in the clinical record. We found 3 patients with borderline IQ and 3 patients with IQ below normal, arithmetic most affected. Seven patients presented quality of life level of 51-60, with greater affectation in social function and body pain, a situation that has improved with the use of enzymatic therapy according to what was referred by the relatives.

Conclusions: Enzyme replacement therapy produces improvement in pain scale, cognitive level and quality of life in children treated at IMSS, which is similar to that reported in international literature.

Keywords

Fabry disease, enzyme replacement therapy, scales.

Resumen

Introducción: La enfermedad de Fabry es una de las enfermedades de depósito lisosomal producida por la deficiencia de la enzima alfa galactosidasa ácida. En la infancia y la adolescencia son características las crisis de dolor paroxístico y acroparestesias.

Objetivo: Reportar características clínicas, escala de dolor, nivel de coeficiente intelectual y calidad de vida en niños con enfermedad de Fabry.

Métodos: Se determinaron las manifestaciones neurológicas más frecuentes mediante historia clínica y exploración neurológica de niños portadores de Enfermedad de Fabry que reciben terapia de reemplazo enzimática en el HG CMN La Raza, de enero a mayo 2016. Se aplicaron encuestas de escala de dolor *Brief Pain Inventory*[4] y calidad de vida SF366, y para el nivel cognitivo se utilizó escala de inteligencia de Wechsler para niños revisada (WISC-R) Escala Verbal.[5]

Resultados: Se incluyeron 12 pacientes con predominio del género femenino (67%). Edad de inicio de manifestaciones neurológicas: masculinos 6.25 años y femeninos 9.12 años. Las manifestaciones neurológicas más frecuentes fueron neuropatía autonómica y sensitiva. Nueve pacientes presentaron dolor neuropático (75%), con mejoría del dolor después de tratamiento según lo informado por los padres en la historia clínica. Se encontraron 3 pacientes con coeficiente intelectual limítrofe y 3 pacientes con coeficiente intelectual debajo de lo normal; el área más afectada fue aritmética. Siete pacientes presentaron nivel de calidad de vida de 51-60, con mayor afectación en función social y dolor corporal, situación que ha mejorado con el uso de terapia enzimática de acuerdo a lo referido por los familiares.

Conclusiones: La terapia de reemplazo enzimática produce mejoría en la escala de dolor, nivel cognitivo y calidad de vida en niños atendidos en el IMSS, lo cual es similar a lo reportado en la literatura internacional.

Palabras clave

Enfermedad de Fabry, terapia reemplazo enzimática, escalas.

Corresponding Author:
Dra. Sofía Lucila Rodríguez-Rivera.
Departamento de Neurología Pediátrica, Centro Médico Nacional La Raza; Calzada Vallejo S/N, Col. La Raza, Delegación Azcapotzalco. Ciudad de México; México. Código Postal: 02990
Tel.: (871) 1 74-85-15.
E-mail: sofiardz85@gmail.com

Introduction

Fabry disease is one of the lysosomal storage disorders, caused by a deficiency of the α-galactosidase A enzyme.[1] There are therapeutic alternatives available for the control of this disease, one of which is enzyme replacement therapy. It is known internationally that this therapy allows to reduce the amount of glycolipids stored in the tissues, modifies neuropathic pain, decreases frequency and intensity of acral pain episodes, stabilizes renal function, and reduces excess cardiac mass, as well as it improves the quality of life and the symptomatology at the digestive level.[2] In Mexico, reports exist only of adult patients treated with enzyme therapy.[3] Information about children is still scarce, and we consider it pertinent to communicate the series of cases of children with Fabry disease that receive enzymatic therapy at the Mexican Social Security Institute. Therefore, we performed a cross-sectional study in which we described clinical characteristics, pain scale, level of IQ, and quality of life in children with Fabry disease who received enzyme replacement therapy.

Methods

A descriptive and cross-sectional study was conducted. The study included 12 children with Fabry disease receiving enzymatic therapy in La Raza General Hospital at the National Medical Center in Mexico City, in the period from January to May 2016. Patients who agreed to participate underwent the usual physical examination in an external consult. In two subsequent appointments, the Brief Pain Inventory[4] was applied to assess pain at its average and maximum expression, rating it as mild (0-3), moderate (4-7), or severe (8-10). The Wechsler Intelligence Scale for Children—Revised (WISC-R) Verbal Scale[5] was applied to evaluate the cognitive level under the supervision of a collaborating neuropsychologist. Scale scores are determined as very superior (130 or more), superior (129-120), above average (119-100), average (109-90), below average (89-80), borderline (79-70), mildly impaired (60-50), moderately impaired (49-35), severely impaired (34-20), and profoundly impaired (less than 20). The Short Form Health Survey (SF36)[6] was applied. Standardized in 1996 and validated by J. Alonso *et al*., it allows measuring health-related quality of life across eight domains: physical function, physical role, body pain, general health, vitality, social function, emotional role, and mental health. The items were applied to a scale ranging from 0 to 100, where 0 is the worst result and 100 is the best.

The database was captured in Excel. Average, median, and mode descriptive statistics were performed, as well as the standard deviation of the variables that required it.

Results

A total of 12 patients diagnosed with Fabry disease were admitted to our study during the period from January to May 2016.

The patients' age range was 7 to 16 years, with an average of 12.33 years, 3.39 SD, and a median of 13.5 years. Females predominated with eight patients (67%), males were four patients (33%). Regarding time with neurological manifestations, the children presented a range of 1-12 years, with an average of 4.1 years, 3.29 SD, and a median of 4 years. The range of enzyme replacement therapy was from 3 months to 4 years, with a mean of 2.12 years, 1.12 SD, a mode of 1, and a median of 1.65. (Table 1)

The most frequent clinical manifestations were autonomic and sensory neuropathy in ten patients with Fabry disease.

The paraclinical manifestations found:
A. In skull MRI, the most common were cortical subcortical atrophy (3 patients), thalamic hyperintensities (2 patients), corpus callosum dysgenesis (1 patient), and normality (6 patients).

B. In the EEG the alterations presented included bioelectrical dysfunction (3 patients), paroxysmal pattern, spikes and polyspikes (3 patients), and normality (6 patients). (Figure 1)

In the pain scale,[4] three patients were found to have mild intensity, eight had moderate, and one severe. (Figure 2)

Regarding the cognitive level scale,[5] three patients with borderline IQ were identified, three patients with IQ below average, three patients with average IQ, one patient with IQ above average, and two patients with very superior IQ. (Figure 3)

In the scale of quality of life[6] in patients with Fabry disease, seven patients showed a 51-60 level, with greater affectation in the areas of social function and body pain. (Figure 4)

In the three scales it was possible to identify that the longer they had treatment, the better the improvement in their pain scores, cognitive level, and quality of life; however, it was not possible to know what the baseline was prior to the enzyme therapy because all the children admitted to the study had already been diagnosed and treated with enzymatic therapy when they arrived at our office.

Table 1. Demographic data of patients with Fabry disease.

Demographic data	Current age, years	Sex, M[1]/F[2]	Age of onset of NM[3], years	Time with NM[3], years	Time with ERT[4], years
1	15	M	10	5	3
2	16	F	15	1	3
3	16	M	4	12	2.5
4	7	F	3	4	2
5	13	M	4	9	4
6	15	F	11	4	2
7	15	F	11	4	1.3
8	10	F	8	2	1
9	7	F	6	1	1
10	14	F	10	4	0.25
11	11	F	9	2	0.25
12	9	M	7	2	1

[1] Male
[2] Female
[3] Neurologic Manifestations
[4] Enzyme Replacement Therapy

Figure 1. Neurologic and paraclinical manifestations in patients with Fabry disease (A and B). EEG, Electroencephalography; CNMR, Cardiac Nuclear Magnetic Resonance.

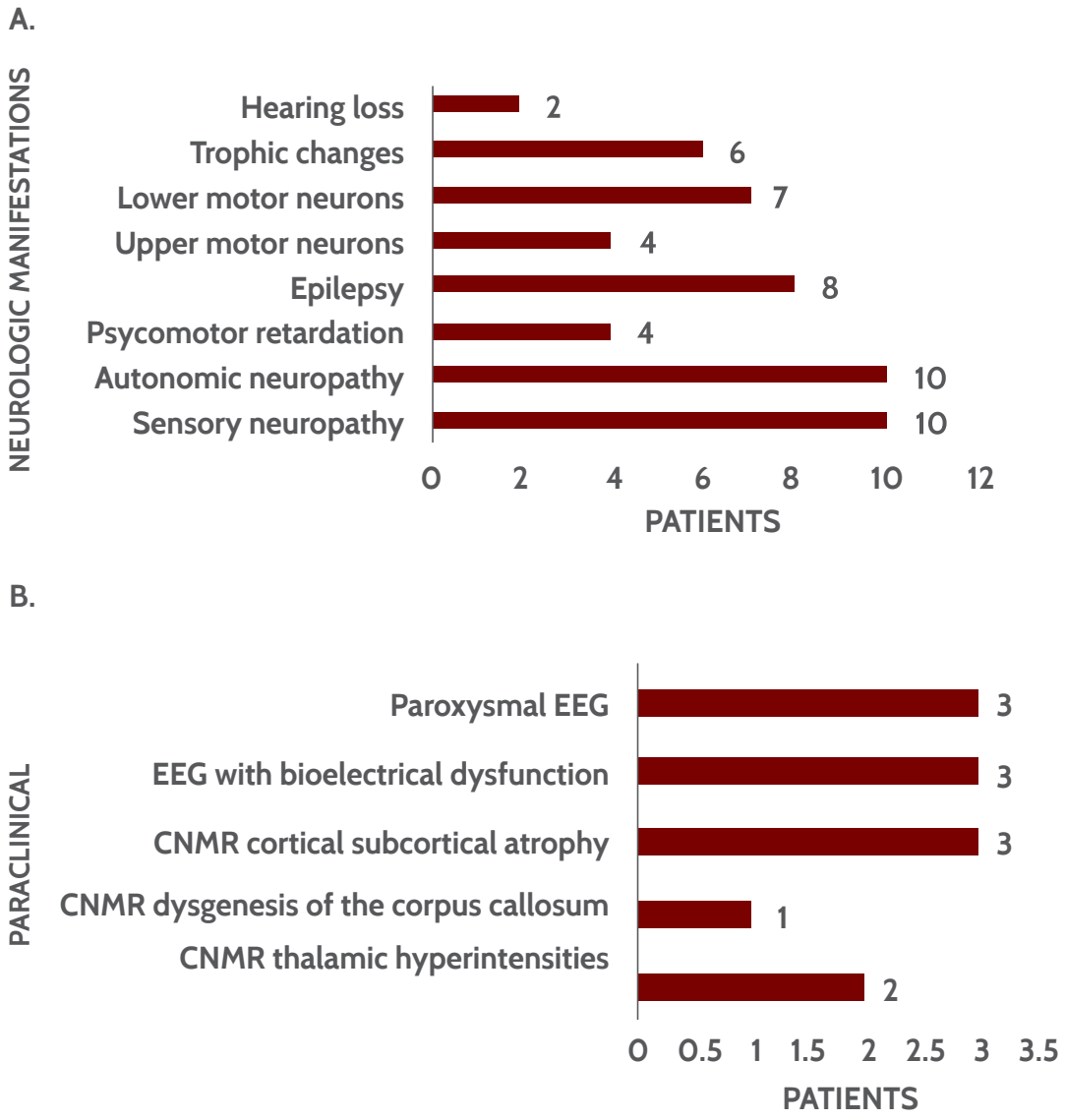
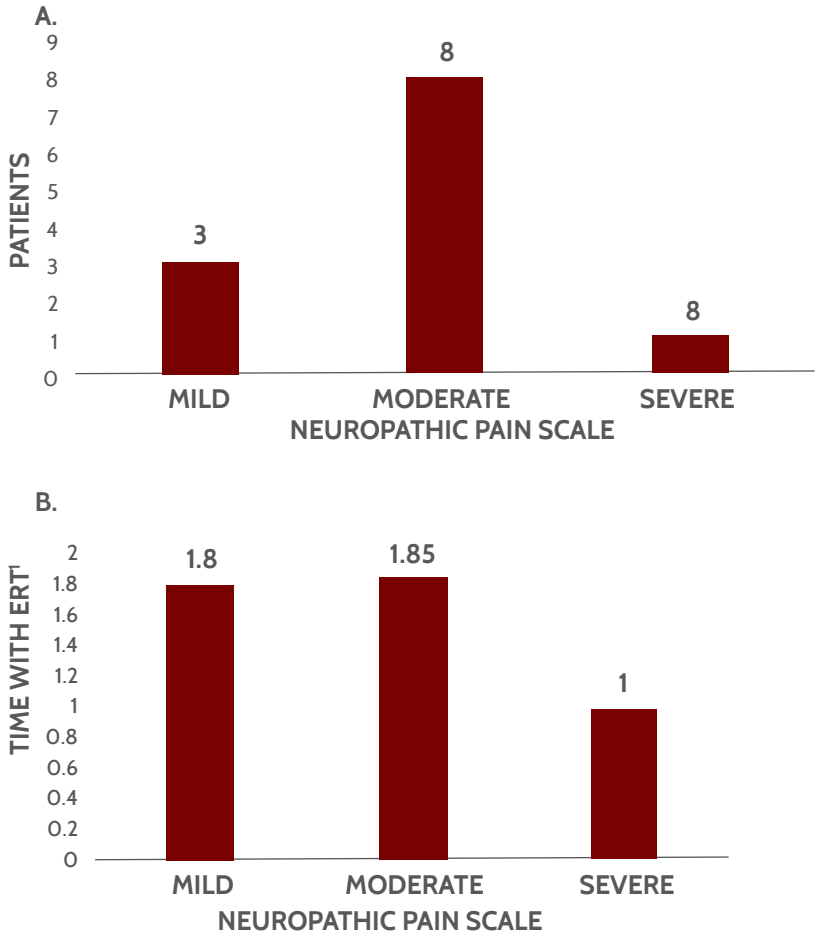
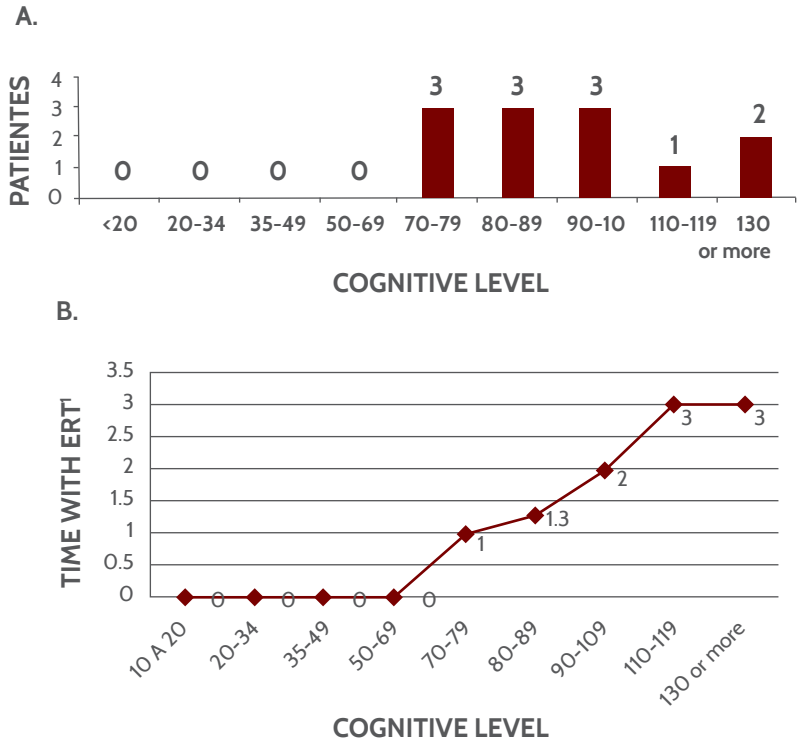


Figure 2. Pain scale in relation to time with enzyme replacement therapy in patients with Fabry disease (A and B).



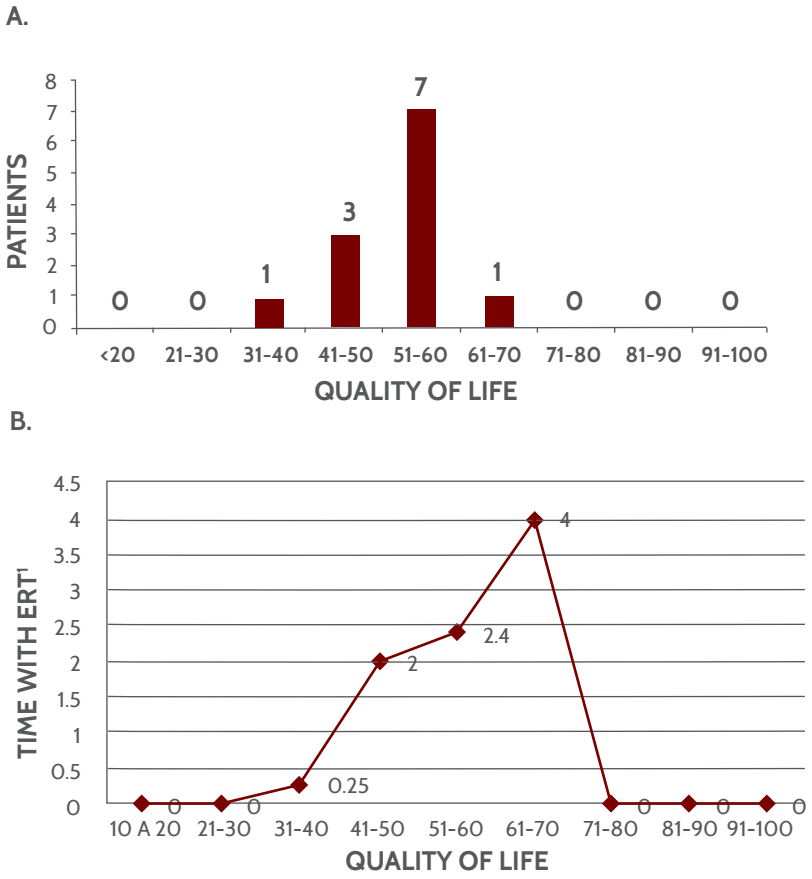
[1]Enzyme Replacement Therapy, years.

Figure 3. Cognitive level scale in relation to time with enzyme replacement therapy in patients with Fabry disease (A and B).



[1]Enzyme Replacement Therapy, years.

Figure 4. Quality of life scale in relation to time with enzyme replacement therapy in patients with Fabry disease (A and B).



[1]Enzyme Replacement Therapy, years.

Discussion

Twelve patients with Fabry disease were included during the period from January to May 2016.

Regarding demographic data, there was a predominance of the female gender with 67% of the cases. In the past it was believed that the disease only affected men and that women were asymptomatic carriers; however, it has been observed that females can also manifest signs and symptoms and they can be as severe as the males'.[7]

The boys presented onset of neurological manifestations in the range of 4-10 years of age, with an average of 6.25 years and a median of 5.5 years. The girls presented onset of neurological manifestations in the range of 3-15 years of age, with an average of 9.12 years and a median of 9.5 years. This coincides with the world literature reports of age of onset in males at 6-10 years, and in females at 8.1-14 years.[8]

Regarding the neurological manifestations in patients with Fabry disease in our study, we observed that the most frequent neurological manifestations were autonomic and sensory neuropathy. This is similar to what was reported by Ries in a 2005 prospective study[9] of children with Fabry disease, in which he showed that the predominant clinical manifestation was neuropathic pain. Furthermore, the systematic review of clinical effectiveness and cost-effectiveness according to Connock in 2006,[10] allows concluding that the administration of enzymatic therapy produces beneficial effects on pain and the sensorineural function of the patient.

In the pain scale,[4] nine patients presented neuropathic pain (75%). The international studies report that neuropathic pain is the most relevant clinical finding in the patient with Fabry disease and constitutes an important cause of disability, absenteeism in the adult population, and hospitalization in the pediatric age.[11] In our study, the pain decreased in the scale with the use of long-term therapy according to what was reported by the relatives of the patients, which coincides with the reports by Eng and by Schiffmann in 2001,[12-15] and Jin-Ho in 2008,[15] who suggested that the administration of enzymatic treatment in patients with Fabry disease produced reduction in pain and improvement in the quality of life of the patients.

At the cognitive level,[5] six patients were identified with a deficit (50%) with greater affectation in arithmetic, presenting improvement in IQ level with long-term treatment. The North American working group of Beguscu et al.[16] in a quasi-experimental study in 2015, found that with enzyme therapy they observed improvement of working memory and of attention in patients in whom cognitive deficit and alteration of executive functions were documented, which correlates with the findings in our study.

In the quality of life scale,[6] seven patients who presented a level of 51-60 with greater affectation in the areas of social function and body pain, showed more improvement the longer they had therapy. A German follow-up study by Hoffmann, *et al*. in 2005,[17] reported that patients with Fabry disease show a deterioration in the quality of life compared to the healthy population, that replacement therapy improves the quality of life scale after one year, and that the improvement becomes more effective after two years. They also report that neuropathic pain is the parameter that most affects the level of quality of life, which coincides with the findings of our study.

Since Fabry's disease is a progressive, early-onset disease, it is a priority to initiate treatment early to avoid situations of irreversible damage.

Early diagnosis, although a challenge, is the key to a good prognosis in Fabry disease since it is a serious, progressive condition that deteriorates the quality of life, leads to an early death, and it's almost always diagnosed when the affectation is very advanced, and the organic and tissue damage is irreversible.

Conclusions

This study observed that enzyme replacement therapy produces improvement of the pain scale, the cognitive level, and the quality of life in patients with Fabry disease who received this treatment in a group of Mexican children in the La Raza General Hospital, which is similar to what is reported in the international literature.[18,19]

Currently, in Mexico, enzyme replacement therapy is available. Though it is costly, its advantages are decisive in improving the patient's quality of life because it modifies the course of the disease and significantly decreases Gb3 concentrations in the early stages. Finally, we consider that other prospective studies that follow up children with Fabry disease are necessary.

Conflicts of interest
The authors declare there are no relevant conflicts of interest in this study.

Funding sources
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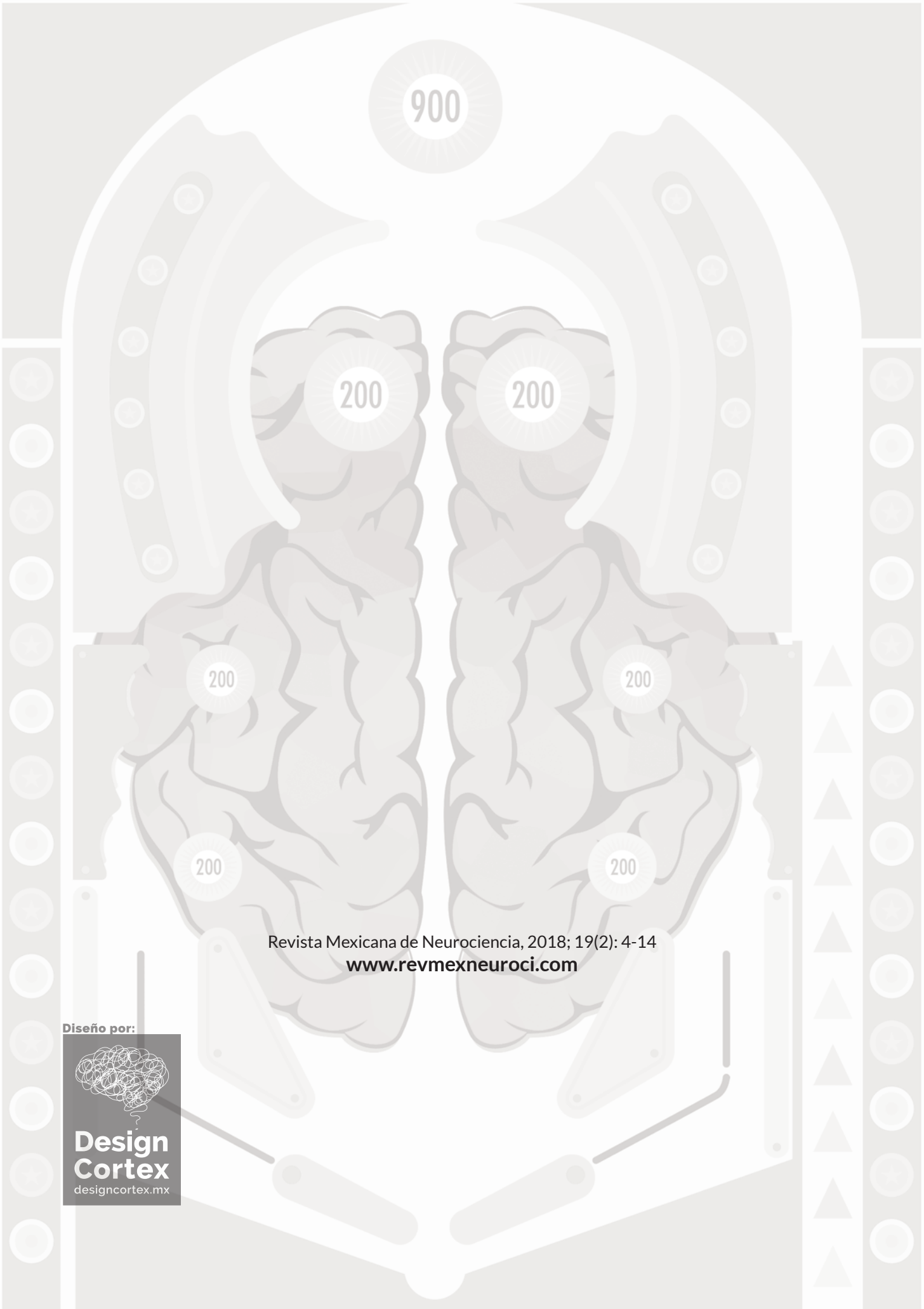

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