Clinical evaluation of diabetic neuropathy in adult patients with type 1 diabetes and its possible association with insulin resistance

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Evaluación clínica de la neuropatía diabética en pacientes adultos con diabetes tipo 1 y su posible asociación con la resistencia a la insulina

Background: In Mexico, there is a lack of information regarding the prevalence and characteristics of Diabetic Neuropathy (DN) in patients with type 1 diabetes (T1D). Although it was, considered as a country with low-incidence of T1D, recent publications show that T1D frequency is under-represented. The aim of this paper is to describe the frequency and severity of DN in patients with T1D using a clinical scale and assess its possible association with insulin resistance.
Methods: We evaluated 48 patients from T1D Clinic. We assessed clinical and biochemical characteristics and determined insulin resistance through estimated glucose dispose rate (eGDR). Patients underwent a neurologic evaluation using a previously validated score.
Results: Seventy-three percent of patients had DN (54% mild and 19% moderate neuropathy). Twenty-nine percent of total population had Metabolic Syndrome. Major predictor factors for DN were the presence of diabetes for more than 13 years (OR 4.6, CI95%: 1.09-15.7), achieving treatment goals during the first 5 years (OR 0.22, CI95%: 0.05-0.87) and eGDR > 7.32 mg/kg/min (OR 0.096, CI95%: 0.011-0.81).
Conclusions: The clinical scale performed in this study is a useful screening tool for DN in adults with long-standing T1D. DN is more frequent in patients with longer evolution of diabetes and poor glucose control during the initial years after diagnosis as expected, but insulin resistance should also be considered as an additional risk factor in this group.

Keywords
Diabetes mellitus, type 1
Diabetic Neuropathies
Metabolic syndrome

Introducción: en México, hay poca información sobre la prevalencia y las características de la neuropatía diabética (DN) en pacientes con diabetes tipo 1 (T1D). Aunque es considerado como un país con baja incidencia de T1D, publicaciones recientes muestran que la frecuencia está subdiagnosticada. El objetivo de este trabajo es describir la frecuencia y gravedad de ND en pacientes con T1D utilizando una escala clínica y evaluar su posible asociación con la resistencia a la insulina.
Métodos: se incluyeron 48 pacientes con T1D. Se evaluaron las características clínicas y bioquímicas, y se determinó la resistencia a la insulina a través de la tasa estimada de eliminación de glucosa (eGDR). Los pacientes fueron evaluados neurológicacamente mediante una escala validada.
Resultados: el 73% de los pacientes tuvieron ND. El 29% de la población total tenía síndrome metabólico. Los principales factores predictores de ND fueron la presencia de diabetes de más de 13 años (OR 4.6, IC95%: 1.09-15.7), lograndо metas de tratamiento durante los primeros 5 años (OR 0.22, IC95%: 0.05-0.87) y eGDR > 7.32 mg/kg/min (OR 0.096, IC95%: 0.011-0.81).
Conclusiones: la escala clínica realizada en este estudio es una herramienta de detección útil para ND en adultos con T1D de larga evolución y pobre control glucémico durante los primeros años posteriores al diagnóstico, pero la resistencia a la insulina también debe considerarse como factor de riesgo.

Palabras clave
Diabetes mellitus tipo 1
Neuropatías diabéticas
Síndrome metabólico

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Diabetic neuropathy (DN) is the most common chronic microvascular complication associated to diabetes.[1] Its prevalence varies between 10 to 90% depending on diagnostic criteria used and the population studied.[2]

Clinically, DN may be asymptomatic or present with a wide spectrum of unspecific manifestations[3] and due to its insidious onset and slow progression, its diagnosis is delayed in most patients.

Pathogenesis of DN includes chronic hyperglycemia, altered microvascular flux, oxidative stress and immune-mediated inflammation. In patients with type 1 diabetes (T1D), the lack of insulin and C-peptide play a main role in the development of neuropathy. In fact, previous studies had shown that insulin has trophic properties in neurons and through inositol 3-phospate/protein kinase B (IP3/Akt) pathway it also regulates oxidative stress. On the other hand, C-peptide regulates Na/K ATPase, nitric oxide synthase and neuronal blood flux. It seems that altered regulation on those mechanisms in T1D patients, induce axon apoptosis and damage of terminal nerves.[3]

In Mexico, there is a lack of information regarding the prevalence and characteristics of DN in patients with T1D. Although it was considered as a country with low-incidence of T1D, recent publications show that T1D frequency is under-represented. Aliss-Samur *et al*. at Centro Médico "La Raza", a tertiary referral center, found that 69% of T1D patients and 95% of T2D patients had DN when surveyed.[4] However, this study lacked information about the risk factors associated with the development of DN. Furthermore, in a previous study we observed that 37 to 44% of our T1D patients were considered to have metabolic syndrome (MS) according Joint Statement Criteria (a junction of criteria proposed by the American Heart Association and the National Heart Lung and Blood Institute AHA/NHLBI) This association has also been called "double diabetes" and is characterized by a pro-inflammatory profile that has been related with higher cardiovascular risk as well as a higher prevalence of chronic complications.[5,6]

The objective of this study was to describe the frequency and severity of DN in adult patients with long-standing T1D and evaluate possible risk factors associated as well as a possible relation with insulin resistance and MS, which have not been previously assessed in these patients.

Material and methods

We conducted a cross-sectional study at a specialized clinic for Type 1 Diabetes (at the Hospital de Especialidades, Centro Médico Nacional Siglo XXI, a tertiary referral center). We included 51 patients with the following characteristics: 18 years of age or older, with at least 10 years from diagnosis and 3 visits per year to the clinic and no change in insulin dose in the last 3 months. Patients previously diagnosed with any type of neuropathy not associated to T1D, those with incomplete records or follow-ups or poor treatment adherence were excluded as well as patients with recent insulin adjustments. The study completed all the requirements of the local ethics committee (Comité Local de Investigación y Ética en Investigación en Salud, with protocol number R-2014-3601-205). The protocol and the aim of the study were fully explained to the subjects, who gave their written consent.

Clinical and anthropometric evaluation

At initial evaluation, we record age at diagnosis of diabetes, if the goals of diabetes control were met during the first five years from diagnosis, if the patient had a history of tobacco use, other comorbidities and previously identified chronic complications of diabetes. We registered weight (kg) and height (meters), as well as waist circumference (WC) in centimeters (cm). Using these parameters we evaluated waist-to-height ratio (WHtR) and waist-to-hip ratio (WHR). A single investigator, using the same calibrated instruments, performed all the anthropometric measurements. WC was determined at the middle point between the inferior rim of the last costal arch and the superior rim of the anterosuperior iliac spine. Body mass index (BMI) was calculated using the formula that divides weight by height to the square. We used BMI determination to define weight groups, according to the World Health Organization (WHO) classification. Blood pressure (Systolic Blood Pressure, SBP and Diastolic Blood Pressure, DBP) was determined in the left arm, after 10 minutes in a resting position, during a fasting state, without coffee or tobacco ingestion in the last week. The sphygmomanometer was calibrated and values were averaged after 2 different measurements with a 5-minute difference between them.

Patients were considered to have good initial control if they fulfilled the following glucose therapy goals during the first 5 years after diagnosis: fasting glucose 80-130 mg/dL, postprandial glucose < 180 mg/dL and glycated haemoglobin (HbA1c) < 7%.

Neurologic evaluation

A single investigator performed the neurological evaluation (CGM) and assigned scores using the previous published score performed by Aliss-Samur

et al.[4] and adapted from Feldman *et al*.[7] Patients' sensibility was evaluated with Semmes-Weinstein monofilament (10 g) applied in foot, hands and arms bilaterally. Patients were tested with closed eyes and were asked to identify site and type of sensation perceived (normal = 0 points; decreased = 0.5 points and absent = 1 point). Vibration perception was evaluated through 128-Hz tuning fork applied in bone prominences at foot, legs, hands and arms bilaterally. In this test, patients were asked to identify the type, intensity and site of sensation perceived (normal = 0 points; decreased = 2 points, and absent = 4 points). Achilles reflex and ankle strength in right and left foot were also evaluated (for normal strength = 0 points; mild weakness = 4 points; moderate weakness = 8 points, and severe weakness = 12 points and for reflexes normal = 0 points; decreased = 3 points, and absent = 6 points). Patients with a final score of 0 were classified as no-neuropathy; a score between 1 to 10 points as mild neuropathy; between 11 to 40 points with moderate neuropathy and more than 41 points as severe neuropathy.

Biochemical determinations

Laboratory results were obtained with a 6 mL blood sample in BD Vacutainer (BD, Franklin Lakes, NJ, USA) and centrifuged at 3150 *x* g for 15 minutes, and serum was divided into two aliquots. We analyzed glucose, cholesterol, c-HDL, and triglycerides with a commercially available kit (COBAS 2010 Roche Diagnostics, Indianapolis, USA) using photocolorimetry with spectrophotometer RocheModular P800 (2010 Roche Diagnostics, Indianapolis, USA). c-HDL samples were treated with enzymes modified with polyethylene glycol and dextran sulphate, analyzed with the same photocolorimetric technique. Glycated hemoglobin was evaluated by turbidimetric immunoanalysis (COBAS 2010 Roche Diagnostics, Indianapolis, USA). Low-density lipoprotein cholesterol (cLDL) was calculated with Friedewald formula c-LDL (mg/dL) = CT mg/dL − (c-HDL mg/dL + triglycerides mg/dL/5) if triglycerides were < 400 mg/dL.[8]

Diagnostic criteria for MS

Patients were considered to have MS when they presented 3 or more of the joint statement criteria from the American Heart Association/National Heart Lung and Blood Institute (AHA/NHLBI) and the International Diabetes Federation (IDF): serum triglycerides > 150 mg/dL (1.7 mmol/L) or patients receiving treatment for hypertriglyceridemia, serum c-HDL < 40 mg/dL (1.03 mmol/L) in men, or < 50 mg/dL (1.29 mmol/L) in women or a previously treated dyslipidemia, arterial blood pressure > 130/85 mmHg in two different determinations or if the patients were receiving treatment with antihypertensive drugs, and WC > 90 cm in men and > 80 in women. Since all the patients were under treatment for T1D, they all had fasting plasma glucose > 100 mg/dL (5.6 mmol/L) at least once.[9]

Insulin resistance quantification

Insulin resistance was calculated using the estimated glucose disposal rate (eGDR) according to the following formula: 24.31 − (12.22 x waist-to-hip ratio [WHR]) − (3.29 x hypertension [defined as 0 = no, 1 = yes]) − (0.57 x HbA1c).[10]

Statistical analysis

Data was analyzed with STATA v.11 and SPSS v.17. Shapiro-Wilk test was used to determine normality. Results are expressed accordingly with means and standard deviations (SD) or medians and interquartile ranges (IQR). To establish associations between quantitative variables, Student's *t*-test or Mann-Whitney *U* test was used. Qualitative variables were associated with chi square or Fisher's test. Receiver operating characteristic (ROC) curves were used to identify the best cut-off point of age at which this ND evaluation test was more useful as well as area under curve (AUC) and 95% confidence intervals. To evaluate the factors associated with the presence of DN, a multiple logistic regression model was performed. A $p < 0.05$ was considered to be significant.

Results

Forty-eight patients fulfilled the inclusion criteria (three patients were discharged due to a detectable C-peptide and family history of diabetes compatible with Maturity Onset Diabetes of the Young, MODY); 73% of them were female. Mean age was 31 ± 10 years and mean age at diagnosis was 12.5 ± 6.6 years. At least 71% of them had family history of type 2 diabetes, 65% had a family member with hypertension, 56% with obesity, 40% dyslipidemia and 29% reported first degree family members with cardiovascular disease. Regarding personal comorbidities 35% of patients had dyslipidemia, 17% hypertension, 19% chronic kidney failure (no more than KDOQI stage 2) and 35% hypothyroid-

ism. Additionally, less than 4% had other autoimmune comorbidities (mainly rheumatoid arthritis and vitiligo). None of these patients had any evidence of cardiovascular diseases. Regard to treatment, 50% of patients had intensive treatment (1 or 2 basal insulin doses with 3 rapid insulin bolus), 35% were on conventional treatment (1 or 2 basal insulin doses with 1 or 2 rapid insulin bolus) and 10% were using insulin pump. Table 1 describes basal characteristics of the total group. There were no differences by gender except in height, however weight and BMI were similar.

tion and neuropathy symptoms. Mean TSH concentration was 2.45 mUI/mL (IQR 1.66-3.93 mUI/mL) with median free thyroxin (fT4) concentration of 1.31 ng/dL (IQR 1.21-1.44 ng/dL). Only nine patients with hypothyroidism had inadequate TSH concentration (7%). However, this did not correlated with the presence or severity of neuropathy (data not shown).

Twenty-nine percent of our patients met MS criteria according to the Joint Statement Criteria.[9] Despite that there were no differences in frequency of MS between patients with or without DN, we observed

Table I Basal characteristics of population by gender

	Total (n = 48)	Female (n = 35)	Male (n = 13)	p
Age, years (mean ± SD)	31.4 ± 9.9	32.7 ± 10.3	27.8 ± 8.0	NS
SBP, mmHg (mean ± SD)	110 ± 16	109 ± 16	115 ± 17	NS
DBP, mmHg (mean ± SD)	71 ± 11	70 ± 11	72 ± 11	NS
WC, cm (mean ± SD)	86 ± 11	86 ± 10	88 ± 12	NS
WHR (mean ± SD)	0.87 ± 0.08	0.87 ± 0.08	0.88 ± 0.07	NS
Weight, kg (mean ± SD)	67.0 ± 13.4	64.4 ± 10.6	74.1 ± 18.1	NS
Height, m (mean ± SD)	1.61 ± 0.11	1.57 ± 0.08	1.74 ± 0.06	< 0.001
BMI, kg/m2 (mean ± SD)	25.6 ± 4.3	26.0 ± 4.1	24.6 ± 5.1	NS
Insulin dose, U/kg weight (mean ± SD)	0.81 ± 0.31	0.82 ± 0.34	0.77 ± 0.28	NS
eGDR, mg/kg/min (mean ± SD)	8.83 ± 2.83	8.44 ± 2.37	9.86 ± 3.73	NS
eGDR < 7.32 (% of patients)	33.3	34.3	30.8	NS

SD = Standard deviation; NS = Not significant; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; WC = Waist circumference; WHR = Waist-to-hip ratio; BMI = Body mass index; eGDR = Estimated glucose dispose ratio. Data analyzed with Student t test

Patients had a median HbA1c 8.8% (IQR 7.8-9.9%), plasma glucose 161 mg/dL (IQR 87-229 mg/dL), cholesterol 198 mg/dL (IQR 167-228 mg/dL), c-HDL 56 mg/dL (IQR 48-66 mg/dL), c-LDL 119 mg/dL (IQR 88-152 mg/dL) and triacylglycerol 111 mg/dL (IQR 81-161 mg/dL). Forty-seven patients had vitamin D deficiency, with a median concentration of 17 ng/mL (IQR 12-21 ng/mL) and one patient had undetectable concentrations of vitamin D. On table 2 we compared biochemical and anthropometrical characteristics between patients with and without neuropathy. We only found difference in creatinine clearance (calculated through Crockoftt-Gault formula) in patients with DN. Additionally patients with DN were significantly older. According to the results of the clinical scale used, 73% of patients had DN, 54% of them had mild neuropathy and 19% moderate neuropathy. We didn't identify any patients with severe neuropathy with this method.

There were no associations between thyroid func-

that 43% of patients with DN had eGDR lower than 7.32 mg/kg/min, cut-off point used for diagnostic insulin resistance in our population (table 2). We also observed borderline significance in the percentage of hypertension and dyslipidemia among groups. None of the other metabolic or clinical parameters were different between groups.

We used a ROC curve using time since diabetes diagnosis (assessed as the time since diagnosis) to determine the best cut-off points to predict DN in our population. Through this analysis, we determined that the time since diagnosis of 13 years or more had a sensibility of 82%, specificity of 55%, and an area under curve (AUC) of 0.68 as shown in figure 1. Using this cut-off point, 72% of patients where correctly classified. The cut-off points were selected using

Youden index, at which (sensitivity + specificity - 1) is maximized.[11]

Accordingly, 83% of patients with DN had more than 13 years of diagnosis. In addition, we observed

Table 2 Biochemical and anthropometric characteristics of patients with and without DN

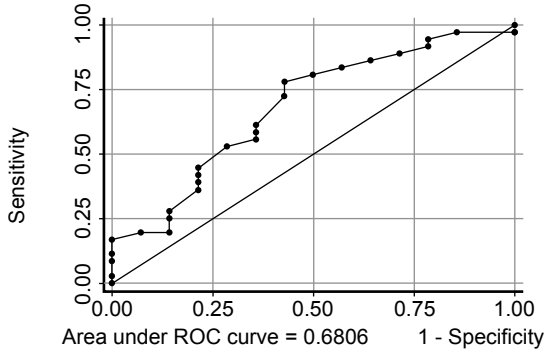
	Without DN (n = 13)	With DN (n = 35)	p
Age, years (mean ± SD)	25.5 ± 8.7	33.1 ± 9.7	0.02
Female sex (%)	62	77	NS
Age at diagnosis, years (mean ± SD)	10.6 ± 6.5	13.2 ± 6.6	NS
Patients with more than 13 years from diagnosis (%)	54	83	0.04
Tobacco use (%)	23	29	NS
BMI, kg/m2 (mean ± SD)	25.5 ± 4.4	25.5 ± 4.3	NS
HbA1c, % (mean ± SD)	8.8 ± 1.2	9.2 ± 1.8	NS
Triacylglycerol, mg/dL (mean ± SD)	103 ± 44	140 ± 74	NS
Cholesterol, mg/dL (median, IQR)	180 (160 - 217)	202 (170-238)	NS
HDL-c, mg/dL (mean ± SD)	58.7 ± 14	54.8 ± 14	NS
LDL-c, mg/dL (mean ± SD)	120 ± 38	118 ± 44	NS
Insulin dose, UI/kg (mean ± SD)	0.97 ± 0.35	0.79 ± 0.33	NS
eGDR, mg/kg/min (mean ± SD)	10.1 ± 3.0	8.3 ± 2.6	0.06
eGDR <7.32 mg/kg/min (%)	7.7	42.9	0.04
Metabolic syndrome (%)	14	36	NS
Glucose control the first 5 years from diagnosis (%)	70	37	0.05
Hypertension (%)	0	23	0.05
Dyslipidemia (%)	15	43	0.04
Hypothyroidism (%)	31	37	NS
Creatinine clearance, ml/min (mean ± SD)	131 ± 37	105 ± 39	0.05
Retinopathy (%)	15	46	NS

HDL-c = High Density Lipoprotein cholesterol; LDL-c = Low Density Lipoprotein cholesterol; eGDR = Estimated Glucose Disposal Rate; MS = Metabolic syndrome; NS = Not significant; SD = Standard deviation, IQR = Interquartile range

that patients with DN had a higher prevalence of failure to reach management goals in the first 5 years.

Finally through a logistic regression analysis we observed that time since diagnosis of 13 years had an OR of 4.6 (95%CI: 1.09-15.7), while the patients that reached therapy goals for diabetes during the first 5 years had an OR of 0.22 (95%CI: 0.05-0.87) and an eGDR higher than 7.32 mg/kg/min had an OR of 0.096 (CI95%: 0.011-0.81).

Figure 1 ROC curve to evaluate DN with time since diagnosis. The ROC curve was performed to evaluate best cut-off point of time since diagnosis associated with DN



Discussion

Type 1 Diabetes is thought to represent 10% of the diabetic population worldwide.[12] Autoimmune diseases are considered to be more prevalent in caucasian population, but recent publications had shown that its incidence is increasing among mestizo groups in Latin America. The correct classification and treatment of type 1 diabetes mellitus in developing countries where access to resources is limited, poses a challenge to the health systems and investigation protocols. The particular comorbidities and complications of T1D are usually not assessed in these patients due to most of them are seemingly asymptomatic, and general practitioners are unaware of associated risk factors and lack of the required time to evaluate them. Additionally, even specialized centers lack of the recommended resources to assess these complications with appropriate gold standards methods. As a consequence, patients are referred to the endocrinologist usually

many years since diagnosis, when most of the complications have been established.[13]

There are a lot of clinical test designed for diagnosis of DN. However, there is a lack of information regarding DN in patients with T1D in our country. In fact, the last study performed for its diagnosis was in 2006 and since then, patients have experimented a demographic transition due to different social influences.[14] For example, we have previously described a high prevalence of T1D patients that fulfill criteria for MS.[5] This association is also called as "double diabetes" and has been related to a higher cardiovascular risk and a higher prevalence of microvascular complications.[15]

We decided to use the clinical scale validated by Aliss-Sumar *et al*. for DN diagnosis in our T1D patients and assess the effect of insulin resistance in the development of DN.[4] We found that 73% of our patients had DN. This prevalence is higher than the reported by Jaiswal *et al*. in T1D patients from the SEARCH cohort (60%), a multi-center study that assessed DN with Michigan's test.[13] We also found that DN affects productive age patients (31.4 ± 9 years), with a mean time since diagnosis of 14 years (14.9 ± 7.9 years) and that comorbidity as hypertension and dyslipidemia influence DN development.

Moreover, previous studies had reported that hypothyroidism is associated with DN.[16] In our study, the prevalence of hypothyroidism was not different between patients with or without DN. However, we identified that hypothyroidism is most prevalent in moderate neuropathy in comparison with patients with mild neuropathy (26% *vs*. 78%, $p = 0.014$). This association could be explained due to an immunological misbalance generated by autoimmunity that impairs synapsis and decreases reflexes, which also increases neuropathic symptoms.

We found that 36% of those patients had MS but this frequency was not different from those without DN. However, a quantitative marker of insulin resistance is calculated eGDR. This marker was validated by Williams *et al*. for its use in T1D patients.[10] and was found to be associated with microvascular complications, as demonstrated by Chillarón *et al*.[17] Among our population, we previously identified that a cutoff point in eGDR < 7.32 mg/kg/min had an 80% sensitivity and 66% specificity for MS diagnosis in our population.[5] Using this same cutoff, we observed that 42.9% of patients with DN had insulin resistance, in comparison with only 7.7% of patients without DN ($p = 0.04$). We elucidated that lack of difference in MS prevalence and total eGDR could be related to the small sample and the high prevalence of metabolic syndrome in our population. However, we consider that the high prevalence of MS in this group of T1D patients (29%) is still noteworthy and it will represent a serious risk factor for future comorbidities. We observed that the main risk factor identified for detecting DN, was a time since diagnosis of more than 13 years. Current clinical guidelines recommend screening 5 years after diagnosis, but these methods are costly and not widely available or are difficult to perform in an everyday care setting.[18] Developing countries also face the limited access to specialized medicine making it necessary to rely on simple clinical tools for screening and diagnosis and to our knowledge, the evolution of peripheral DN in T1D has not been previously evaluated in our country. This scale seems to be a good screening tool for patients recently referred to the specialist with any previous testing for DN. It may also help to classify patients with more severe neuropathy, which require additional evaluation by a neurologist. Interestingly, other microvascular complications as well as metabolic parameters such as HbA1c at the time of the test were not different between patients. This allows us to theorize that nervous tissue is more susceptible to the chronicity of exposure of hyperglycemia and not necessarily to its severity, and that could be related to inflammatory and prooxidative effects of glucose.

We observed a lower prevalence of DN in those patients who meet glycemic goals during the first 5 years from diagnosis. Besides the lower exposure to chronic and severe hyperglycemia, this could be related to the "metabolic memory", a concept that assumes that delay in blood glucose control during the first years from diagnosis will predict a worst course of the disease even decades after diagnosis.[19]

On the other hand, in our population only 37.5% of patients had DN previously detected by neuroconduction test. However, when we applied this clinical scale nearly twice of them reported symptoms related with DN (73%). Furthermore, 88% of patients previously diagnosed, where also detected through the clinical scale. The comparison with another sensitive test tool allows us to ensure that this scale could be reliable for DN screening and that patients with positive results should be evaluated with other methods. This scale also has the advantage of its easy applicability and few requirements in terms of time and training for its application.

Conclusion

DN related to T1D has a clinical behavior and pathophysiology that differ from other neuropathies, including the related to T2D. Our study shows that this disease is highly prevalent in Mexican population and that this could be related with other prevalent factors as

insulin resistance due to overweight and obesity (73% of our general population according to the ENSANUT 2012).[20] We also suggest that frequent, cheap and easily accessible assessment strategies such as this should be implemented for these patients in order to ensure early diagnosis and treatment. Improved health strategies and patient education are also needed in order to achieve tighter glycemic control targets, especially during the early years of diagnosis, where tertiary prophylaxis can still be useful.

Conflicts of interest: All of the authors have filled and sent the translated-to-Spanish form of the declaration of potential conflicts of interest of the International Committee of Medical Journal Editors, and it was not reported any conflict with regards to this article.

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