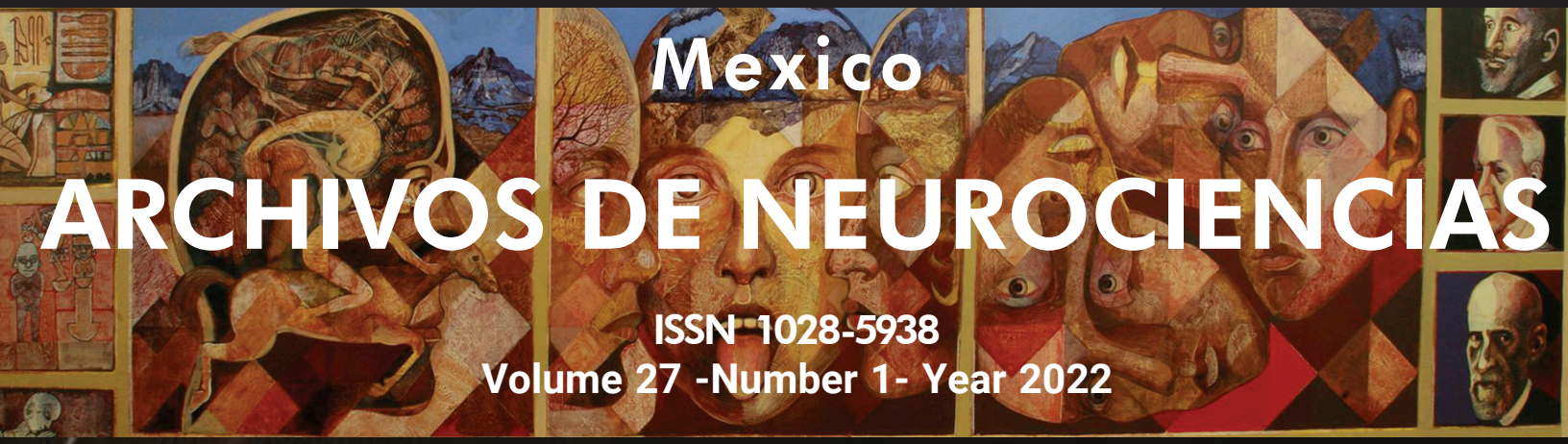

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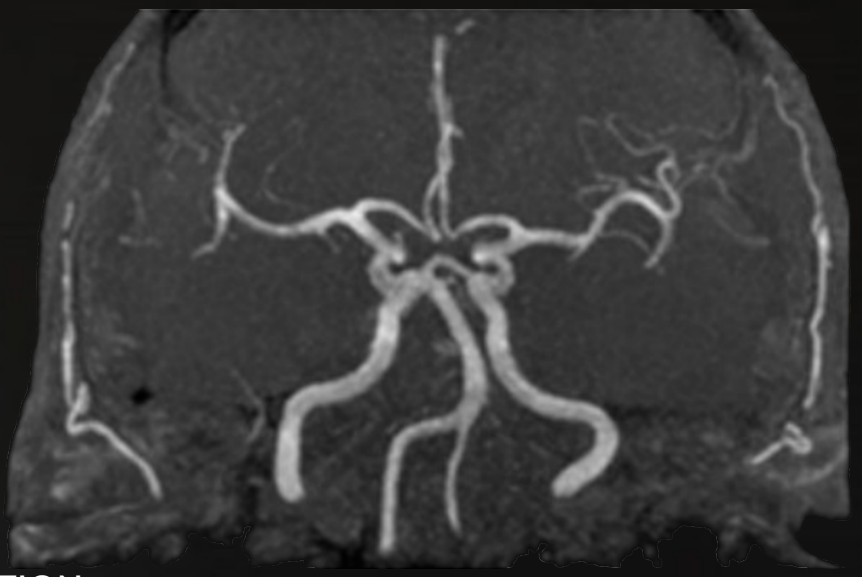

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Validation and standardization of neuropsychological tests for the evaluation of praxias and gnosias in university students (Evaluation of praxias and gnosias)

Puerta-Lopera Isabel Cristina[1] | Dussán-Lubert Carmen [2] | Montoya-Londoño Diana Marcela [3]
Landínez-Martínez Daniel [4] | Pérez-Parra Julio Ernesto [5]✉

1. Vicerrectora de investigaciones, Universidad Católica Luis Amigó, Colombia.
2. Department of Mathematics, University of Caldas, Colombia.
3. Department of Educational Studies, University of Caldas, Colombia.
4. Catholic University Luis Amigó and University of Manizales, Colombia.
5. Department of Human Movement, Autonomous University of Manizales, Colombia.

Correspondence

Julio Ernesto Pérez-Parra
Department of Human Movement, Autonomous University of Manizales, Colombia.

✉ jeperez@autonoma.edu.co

Abstract

Introduction: Most specialized literature focuses on the study of cognitive functions regarding brain injuries, which can relate to why praxias and gnosias are rarely discussed from a normality perspective. Objective: This article describes the results from a validation and standardization study of tests for the evaluation of praxias and gnosias.
Material and methods: 208 healthy university students were evaluated. The following tests were validated and standardized: Rey–Osterrieth Complex Figure Test (copy) and visual retention test, visual discrimination and orientation judgment (Benton test). The following tests and analyzes were performed: appearance validity (expert judgment), content validity (factor analysis), concurrent criterion validity (correlation coefficient), internal consistency (Omega coefficients) and intra- and inter-rater reliability (proportion of correct answers, correlation coefficient and comparison of paired medians).
Results: Adequate content validity was evidenced in all tests; adequate criterion validity in praxis evaluation measures; low criterion validity, internal consistency and test – retest reliability for gnosias and praxias tests. Conclusions: It is advisable to use the most appropriate test according the cultural context in which it is applied, as well as standardized instruments for the target population.

Key words: *praxias, gnosias, young adult, neuropsychological tests, reproducibility of results, reference standards.*

Introduction

Mental functions are complex functional systems, not located in restricted areas of the cortex or in isolated cell groups, but organized in systems of areas that work in concert. Each of these areas plays a role within the complex functional system, and can be located in completely different regions in the brain, very distant from each other;[1] these systems represent the basis of gnosias and praxias. The terms gnosis and praxia were first introduced by Ludwig Edinger, a German neurologist considered the founder of neuroanatomy, and were later adopted by Hugo Liepmann in the psychological description of agnosia and apraxia.[2]

Luria had previously stated that, in the case of gnosis, the main contribution is made by the Second Functional Unit of the brain, whose primary function is the reception, analysis and storage of information.[3] This unit is located in the lateral regions of the neocortex, on the convex surface of the hemispheres, of which it occupies the posterior regions, including the visual (occipital), auditory (temporal), and general sensory (parietal) regions. From this perspective, gnosis is defined as the ability to recognize a stimulus, regardless of whether the sensation of it is adequate; consequently, it represents the ability to transform sensation into perception.[4] Considering this, in a diagnosis of agnosia, although a subject can see, hear and feel, they cannot recognize visual, auditory or tactile stimuli. Furthermore, it is not possible to speak of gnosis without a related cognitive ability, praxis. These constitute the ability to carry out a programmed and organized movement with a specific purpose in a defined sequence, and to execute it in an intentional and coordinated manner.[5] It could be affirmed that there is no praxis without gnosis, that is, there is no intentional, adapted, effective and efficient execution of an action without the previous or simultaneous mental representation of it. Praxias are then considered a complex integrative process between the knowledge of something and its representation, and the corresponding actions, so that they are adequate and efficient for its adaptive exteriorization.[6]

According to recent studies, in the Colombian context, Ardila et al. standardized the Rey-Osterrieth Complex Figure Test for the evaluation of gnosis and praxis through two normative studies.7 In the first one, the influence of the educational level of the participants was considered: the test was applied to two groups of 100 different subjects (schooled and non-schooled). Subsequently, the subjects were divided by gender and age into five age ranges: 16-25, 26-35, 36-45, 46-55, 56-65. In the second, the influence of age on test performance was analyzed. In this study, 346 subjects over 55 years of age (with and without brain damage) were included. In this standardization, normative data were presented for each of the tests according to age, years of schooling and differences by sex. In addition, results of the population with brain damage were integrated.[7]

Also noteworthy is the Child Neuropsychological Evaluation (ENI) standardization,[8] carried out with children between 5 and 16 years of age in Mexico and Colombia, in which tasks related to visual-constructive skills – that included figure, complex figure and human figure copying – were created and standardized. Regarding visual perception, tasks of superimposed images, blurred images, visual closure, and integration of objects were performed. Pertainig spatial abilities, tasks of right-left comprehension and expression, drawing from different angles, orientation of lines and location of coordinates were carried out. Norms for each task according to age range were presented.[8]

Another study, carried out with 141 children from Bucaramanga (Colombia) of both sexes, between 9 and 16 years old,[9] standardized the Benton Visual Retention and Judgement of Line Orientation tests and the Rey-Osterrieth Complex Figure Test (Copy score). The analysis by age was presented according to two groups, the first from 9 to 12 years old, and the second from 13 to 16. Normative data were reported according to age, education level, and sex.

Neuronorma[10] project estudied a sample of 179 normal subjects and obtained normative data on the Spanish population between 18 and 49 years of age. Neuropsychological tests of widespread use were applied: Benton Judgement of Line Orientation, Rey-Osterrieth Complex Figure and some subtests from the Visual Object and Space Perception Battery (VOSP). Demographic features and sociocultural characteristics were recorded and normative data by age, education level and gender were described.[10]

More recently, a neuropsychology research carried out in Colombia with 1425 healthy adults standardized the Rey-Osterrieth Complex Figure Test. Normative data was established according to age, educational level, and sex.[11]

The standardization of neuropsychological and psychological tests, adapted to age ranges, and sociocultural contexts, is essential to more precisely characterize the target population. In this research, the university population was characterized in terms of their cognitive functioning, with the objective of having accurate normative data for the elaboration of descriptive

profiles of cognitive functioning of said population in urban environment, which will lead to the design of evaluation proposals and intervention actions relevant to the specific characteristics of the context of the young people evaluated.

In 2021, Manizales, Colombia, was a university town of 450,074 inhabitants, of whom 76,251 were between the ages of 16 and 26 (17% of the population).[12] The city had a university population of 61,662 students, 84% of them enrolled in face-to-face mode and 83% in undergraduate programs; which averages eleven university students for every 100 inhabitants.[13] These figures highlight the importance of the neuropsychological characterization of the population under study in said context.

The objective of this research was to validate and standardize the following tests in university students between 16 and 26 years of age in the city of Manizales, Colombia: the Rey-Osterrieth Complex Figure Test, and Benton Visual Retention, Visual Form Discrimination and Judgement of Line Orientation tests.

Material and methods

This study is part of a macroproject, in which other neuropsychological functions tests were validated and standardized for the same population – such as attention, language, memory and self-concept –[14-17] and it was approved by the University of Caldas, Colombia (code 0201712), following the guidelines of Resolution 8430 of 1993 of the Colombian Ministry of Health, which establishes the scientific, technical, and administrative standards for health research.

Sample

A validation study was carried out with 208 student volunteers from the University of Caldas and the University of Manizales, Colombia, with a mean age of 21 years (SD 2.8 years). The following inclusion criteria were applied: age between 16 and 26 years, absence of neurological or psychiatric alterations or school failure; and manifestation of informed consent. Volunteers were excluded for any of the following criteria: neurodevelopmental disorders; clinical history with signs and symptoms of focal or diffuse cognitive impairment; history of central nervous system diseases with neuropsychological difficulties; perceptual disorders – visual, auditory and/or motor – that could affect the neuropsychological evaluation; presence of uncontrolled acute or chronic systemic diseases that interfere with the neuropsychological evaluation; a history of alcohol or drug abuse in the last 5 years, and a history or presence of a major psychiatric disorder. Calculation of the sample size. For the correlational analysis tests (concurrent validity and intra- and inter-rater reliability), the Hernández-Sampieri et al. (2010) criterion was applied for a minimum correlation expected of 0.21,[18] with a confidence level of 95%, and a statistical power of 85%, for a minimum sample of 201 participants.

For the reliability tests, 7 participants were assigned for each item, taking as reference the instruments with the most items: Benton Visual Retention Test (30 designs) and Benton Judgement of Line Orientation Test (30 stimuli), for a calculated sample of 210 participants.

Instruments

a. Rey-Osterrieth Complex Figure Test: it was developed by Rey and Osterrieth,[19,20] and translated into English by Corwin and Bylsma.[21] It assesses a wide variety of cognitive processes, including planning, organizational skills, problem-solving strategies, as well as perceptual and motor functions, and episodic memory.[22-25] It consists of 18 items.

b. Benton Visual Retention Test: it is an individually administered test for people eight years of age and older, which evaluates visual perception, visual memory and visuo-constructional abilities. It is made up of 3 sets or forms of 10 designs (8,5×5,5 inches) that measure the examinee's visual and memory abilities, as well as a set of alternative designs for repeated tests. The examinee is given a booklet containing 10 blank pages on which designs are reproduced. There are two forms of administration for this test: through drawing or multiple choice answers. The drawing option contains 3 alternate forms (C, D and E). Each one is made up of 10 designs; the first two consist of a geometric figure, and the rest of two main figures and one smaller figure. There are four main types of administration. In Administration Type A, which is the most standardized type, each design is presented for 10 seconds and then removed, immediately after the subject is asked to reproduce the drawing from memory on a sheet of paper at their own pace. Administration Type B is similar to Administration Type A except that each pattern is presented for only 5 seconds. Administration Type C (Copy) requires the subject to copy each of the designs without removing the stimulus from view. In Administration Type D each design is presented for 10 seconds and the subject must reproduce it after a 15-second delay. In the present investigation, the Administration Type A was used.[26,27]

c. Benton Judgment of Line Orientation Test: This is a 30-stimulus test that assesses visuospatial perception through the comparison of spatial relationships between line segments[28-29]. For each item the subject is asked to match a pair of lines with two of eleven lines presented in a semicircular model.29 Score is based on the sum of items in which there was a correct answer for both lines.[27]

d. Visual Form Discrimination Test: it is a brief test consisting of 16 multiple-choice items,[28] which involves the abilities of scanning and complex visual discrimination, but not memory.[30] Participants must maintain their visual attention throught a search process.[28] Each section of the test consists of a multiple response stimulus with 4 options, each of them containing two main figures and a smaller one. The four stimuli indicate: **1**. correct reproduction of the original figure (correct); **2**. rotation (displacement) of the figure (error pattern); **3**. rotation of the main figure; or **4**. distortion of the main figure. Total score is obtained by assigning two points for each correct answer and one point in case there is a peripheral error; other types of errors get cero points. The maximum score is 32 points.

Analysis plan

- Normality of the data was confirmed by a Shapiro Wilk test.
- Face validity: five experts in neuropsychology were consulted, using a consensus methodology. The previously selected instruments and tests were submitted for discussion.
- Content validity: factor analysis of principal components was conducted with rotation oblimin with Kaiser and maximum number of interactions for convergence 25. Sample adequacy conditions (KMO=.85) and sphericity p<.0001) were satisfactorily met. The tests were applied to a group of 50 people to determine correct understanding, rectify language difficulties and establish standard application and scoring criteria.
- Concurrent criterion validity: Spearman's correlation coefficient was used, since variables were not normally distributed. The performance of the students in TFCRO, TRVB, TOLB and TDVB was compared against the one showed in different criterion tasks taken from the Neuropsi Battery,[31] and some subtests of the Neuropsychological Assessment Battery for adults (NAB).[32] In the case of the TFCRO copy,[15] the coding task was used as a criterion – visuospatial process complex figure coping.[31] For the TRVB, TOLB and TDVB tasks, the subtests of perception and spatial orientation of the visuospatial area evaluation from the Neuropsychological Assessment Battery for adults (NAB) were used as criterion tasks.[32]
- Internal consistency was determined with the Omega coefficient.
- Intra- and inter-rater reliability: consistency related to the application time (test-retest) and the application by different evaluators. The Wilcoxon test for paired medians and Spearman's rank correlation coefficient were carried out using correct answers proportion. In the case of intra-rater reliability, 50 of the 208 students were randomly selected and took the test again 4 months later.
- The percentage of correct answers (pre and post) for each item was obtained using the binomial proportion p. A difference between responses of up to 20% was established as acceptable. Additionally, the pre-test and post-test results were compared using the Wilcoxon test for paired medians and Spearman's rank correlation coefficient.
- Scales for each of the tests: normative data for each of the tests were calculated. Direct scores and percentiles are presented. First, normality of the data was established and, subsequently, it was analized if there was a difference in the mean responses according to gender (using the Student's t-test or the Mann–Whitney U). No differences were found in most of the tasks to evaluate praxis and gnosis, with the exception of TOLB. As a result, only for this variable, a scale broken down by gender is shown.

Results

Face validity. The five experts in neuropsychology agreed on the usefulness and relevance of the preselected instruments and tests according to the stated objective, for which the following instruments with their corresponding tasks and items were used:

Praxias:
Rey-Osterrieth Complex Figure Test - TFCRO
-Copy score - TFCRO PC
-Copy time - TFCRO TC
-Memory time - TFCRO TM
-Deferred average score - TFCRO PMD
Gnosias:
Benton Visual Discrimination Test - TDVB
-Total score - TDVB TP
Benton Judgment of Line Orientation Test - TOLB
- Total correct answers - TOLB TC
Benton Visual Retention Test - TRVB
-Form C - TRVB FC
-Form D - TRVB FD
-Form E - TRVB FE
-Total correct answers - TRVB TRC

Content validity. Factor analysis of principal components was performed; in the case of gnosis, the first two factorial axes retain 64.2% of total variance and TRVB saturates the first axis, while TOLB does so in the second axis (Table 1).

In the case of praxis, it was again found that the first two factors explained 62.9% of the total variance and that the copy score and deferred memory score explained axis 2, in turn, deferred memory and memory times explain the first axis (Table 1).

Concurrent criterion validity. With the exception of TFCRO vs. coding (praxias), no significant correlations were found between the tests evaluated and the batteries taken as reference (Table 2).

Internal consistency. Table 3 shows adequate Omega coefficients for the tasks of cognitive processes of praxis and gnosis, with greater homogeneity in the latter.

Intra-rater reliability (test–retest). The percentage of correct answers showed agreement greater than 60% in most of the evaluated items, which indicates that the results of the scales applied at different times remain stable. In most subtests, the differences between medians and correlations were statistically significant, indicating adequate test-retest agreement or intra-rater reliability (Table 4).

Table 1. Factor saturation for content validity

Process	Item	Factor 1	Factor 2
Gnosias	TDVB TP	0,011	0,845
	TRVB FC	0,766	-0,161
	TRVB FD	0,688	-0,005
	TRVB FE	0,744	-0,026
	TRVB TRC	0,991	-0,081
	TOLB TC	0,347	0,625
	% explained variance	**45,2**	**19,0**
	% cumulative variance	**45,2**	**64,2**
Praxias	TFCRO PC	-0,297	-0,684
	TFCRO TC	-0,818	0,245
	TFCRO TM	-0,814	0,250
	TFCRO PMD	-0,315	-0,640
	% explained variance	**37,9**	**37,9**
	% cumulative variance	**25,0**	**62,9**

Abbreviations. **TDVP**: Benton Visual Discrimination Test; **TRVB**: Benton Visual Retention Test; **TOLB**: Benton Judgment of Line Orientation Test; **TFCRO**: Rey-Osterrieth Complex Figure Test; **TP**: Total score; **FC**: Form C; **FD**: Form D; **FE**: Form E; **TRC**: Total correct answers; **TC**: Total correctas; **PC**: Copy score; **TC**: Copy time; **TM**: Memory time; **PMD**: Deferred average score.

Table 2. Correlation coefficients for concurrent criterion validity

Process	Crossed items	Spearman	pValue
Gnosias	TDVB TP – Visuospatial area. Visual perception	-0,172	0,232
	TOLB TC – Visuospatial area. Visual perception	-0,083	0,566
	TRVB FC – Visuospatial area. Visual perception	-0,002	0,991
	TRVB FD – Visuospatial area. Visual perception	-0,053	0,712
	TRVB FE – Visuospatial area. Visual perception	0,053	0,713
	TRVB TRC – Visuospatial area. Visual perception	0,064	0,657
	TDVB TP – Spatial orientation	-0,017	0,906
	TOLB TC – Spatial orientation	0,161	0,263
	TRVB FC – Spatial orientation	0,122	0,396
	TRVB FD – Spatial orientation	0,233	0,103
	TRVB FE – Spatial orientation	0,191	0,183
	TRVB TRC - Spatial orientation	0,261	0,068
Praxias	TFCRO PC - Codification	0,296	0,037
	TFCRO TC - Codification	0,022	0,880

Abbreviations. **TDVP**: Benton Visual Discrimination Test; **TRVB**: Benton Visual Retention Test; **TOLB**: Benton Judgment of Line Orientation Test; **TFCRO**: Rey-Osterrieth Complex Figure Test; **TP**: Total score; **FC**: Form C; **FD**: Form D; **FE**: Form E; **TRC**: Total correct answers; **TC**: Total correctas; **PC**: Copy score; **TC**: Copy time; **TM**: Memory time; **PMD**: Deferred average score.

Table 3. Omega coefficient for internal consistency

Process	Item	Coefficient value
Gnosias	TDVB TP, TOLB TC, TRVB FC, TRVB FD, TRVB FE, TRVB TRC	0,79
Praxias	TFCRO PC, TFCRO TC, TFCRO TM, TFCRO PMD	0,67

Abbreviations. **TDVP**: Benton Visual Discrimination Test; **TRVB**: Benton Visual Retention Test; **TOLB**: Benton Judgment of Line Orientation Test; **TFCRO**: Rey-Osterrieth Complex Figure Test; **TP**: Total score; **FC**: Form C; **FD**: Form D; **FE**: Form E; **TRC**: Total correct answers; **TC**: Total correctas; **PC**: Copy score; **TC**: Copy time; **TM**: Memory time; **PMD**: Deferred average score.

Table 4. Test–retest agreement for intra-rater reliability

Cognitive process	Item	Hit percentage	pValue median difference	Spearman correlation coefficient	pValue coefficient
Gnosias	TDVB TP	0,68	0,109	0,389	<0,01
	TRVB FC	0,80	0,000	0,058	0,695
	TRVB FD	0,80	0,004	0,283	0,052
	TRVB FE	0,78	0,340	0,168	0,253
	TRVB TRC	0,76	0,007	0,235	0,099
	TOLB FH	0,80	0,001	0,579	<0,01
Praxias	TFCRO PC	0,66	0,662	0,195	0,174
	TFCRO TC	0,24	0,001	0,451	<0,01
	TFCRO TM	0,60	0,253	0,430	<0,01
	TFCRO PMD	0,78	0,000	0,105	0,467

Abbreviations. **TDVP**: Benton Visual Discrimination Test; **TRVB**: Benton Visual Retention Test; **TOLB**: Benton Judgment of Line Orientation Test; **TFCRO**: Rey-Osterrieth Complex Figure Test; **TP**: Total score; **FC**: Form C; **FD**: Form D; **FE**: Form E; **TRC**: Total correct answers; **TC**: Total correctas; **PC**: Copy score; **TC**: Copy time; **TM**: Memory time; **PMD**: Deferred average score.

Inter-evaluator reliability (application by different evaluators). All tests showed high concordance between evaluators, which indicates equivalence in the measurements by different evaluators; although in TOLB medians show divergent measurements (Table 5).

Table 5. Reliability related to the application by different evaluators (inter-rater reliability)

Cognitive process	Two evaluators	Hit percentage	pValue median difference	Spearman correlation coefficient	pValue coefficient
Gnosias	TDVB TP	0,977	1,000	0,995	0,000
	TRVB FC	0,849	0,000	0,912	0,000
	TRVB FD	0,822	0,000	0,929	0,000
	TRVB FE	0,826	0,000	0,913	0,000
	TRVB TRC	0,730	0,000	0,942	0,000
	TOLB FH	0,973	0,152	0,992	0,000
	TOLB FV	0,977	0,506	0,996	0,000
	TOLB TC	0,954	0,134	0,997	0,000
Praxias	TFCRO PC	0,931	0,533	0,833	0,000
	TFCRO TC	0,969	0,782	1,000	0,000
	TFCRO TM	0,958	0,488	0,956	0,000
	TFCRO PMD	0,865	0,231	0,451	0,000

Abbreviations. **TDVP**: Benton Visual Discrimination Test; **TRVB**: Benton Visual Retention Test; **TOLB**: Benton Judgment of Line Orientation Test; **TFCRO**: Rey-Osterrieth Complex Figure Test; **TP**: Total score; **FC**: Form C; **FD**: Form D; **FE**: Form E; **TRC**: Total correct answers; **TC**: Total corrects; **PC**: Copy score; **TC**: Copy time; **TM**: Memory time; **PMD**: Deferred average score.

Scales. Tables 6 and Table 7 show normative data for the population studied: direct scores and percentiles. There were no significant ceiling or floor effects that required further analysis. As mentioned in the methods section, only the TOLB-Copy Time test is presented by gender, since no significant differences were found in any other tests ($p>0.050$).

Table 6. Rey's Complex Figure Test and Benton's Visual Shape Discrimination Test. Direct scores and percentiles for university students between 16 and 26 years old

Percentile	Direct scoring				
	TFCRO PC	TFCRO TC	TFCRO TM	TFCRO PMD	TDVB TP
99	36	370	269	36	-
95	36	255	187	34	-
90	36	193	168	33	-
85	36	171	152	32	-
80	36	153	147	30	-
75	36	138	138	30	32
70	36	133	131	28	31
65	36	125	124	27	-
60	36	120	117	27	-
55	36	115	111	26	-
50	36	112	106	26	30
45	35	108	102	25	-
40	35	100	98	24	29
35	35	98	94	23	-
30	35	94	88	22	28
25	34	90	84	21	27
20	34	87	79	20	-
15	33	84	70	20	26
10	32	77	62	18	24
5	31	61	54	16	22
1	28	49	36	10	17
N	208	208	208	208	207
Media	34,8	126,7	115,5	26,4	28,7
Standard deviation	1,9	63,5	59,1	16,9	3,4

Abbreviations. **TFCRO**: Rey-Osterrieth Complex Figure Test; **TDVP**: Benton Visual Discrimination Test; **PC**: Copy score; **TC**: Total corrects; **TC**: Copy time; **TM**: Memory time; **PMD**: Deferred average score; **TP**: Total score.

Table 7. Benton's Visual Retention Test (TRVB) and Benton's Line Orientation Judgment Test (TOLB). Direct scores and percentiles for university students between 16 and 26 years old

Percentile	Direct scores					
	TRVB Forma C	TRVB Forma D	TRVB Forma E	TRVB Total correct answers	TOLB TC	TOLB TC Hombres
99	-	-	-	30	56	60
95	-	-	-	29	55	58
90	10	-	-	-	54	56
85	-	10	-	28	53	56
80	-	-	-	-	52	55
75	-	-	-	27	51	54
70	-	9	10	-	50	52
65	9	-	-	26	49	52
60	-	-	-	-	48	51
55	-	-	-	-	47	50
50	-	-	-	25	46	49
45	-	8	9	-	45	48
40	8	-	-	24	43	48
35	-	-	-	23	43	47
30	-	-	-	-	41	47
25	-	7	8	22	40	45
20	7	-	-	21	39	42
15	-	6	7	-	35	41
10	6	-	-	20	33	39
5	5	5	6	18	30	36
1	4	4	4	15	24	30
N	208	208	208	208	125	83
Media	7,9	7,7	8,4	24,0	46,1	48,5
Standard deviation	1,5	1,7	1,5	3,4	8,3	6,9

Abbreviations. **TRVB**: Benton Visual Retention Test; **TOLB**: Benton Judgment of Line Orientation Test; **TP**: Total score; **TC**: Copy time

Discussion

Praxias and gnosis are probably among the least studied cognitive functions, this is perhaps due to the fact that the specialized literature focuses on their study only in the case of brain injuries and not from a normal perspective, as well as the wide repercussion these alterations have in the development of reading, writing and mathematical processes, in addition to some types of dementia, among which frontotemporal dementia stands out.[37,38]

The term praxia refers to a system of coordinated movements articulated to achieve an objective, which are characterized for being sequential, learned and not instinctive or reflexive. According to this perspective, the term apraxia refers to the detected deficit in making voluntary movements associated with objects in the absence of paralysis. Moreover, apraxia has been traditionally defined as a difficulty in executing learned gestural skills or motor acts despite the preservation of motor and sensory systems, coordination, comprehension, as well as adequate collaboration.[39,40] Currently, it is considered as any acquired deficit of motor skills in the absence of motor alterations, which occurs as a result of neurological dysfunction.[39,40]

Gnosias refer to the sensory-perceptive recognition capacity that involves different inputs (visual, auditory, tactile, and gustatory). In turn, agnosias are defined as the inability to consciously recognize sensory stimuli of a certain type, that cannot be attributed to a sensitive alteration, nor to a verbal or intellectual deterioration.[37] The union of manual praxias and visuospatial gnosic aspects determine the formation of constructive praxias.

In terms of assessed praxias, results show adequate content validity, concurrent criterion and reliability related to test application by different evaluators; as well as adequate content validity and reliability related to the application by different evaluators in the case of gnosis.

Gnostic tasks have adequate content validity. These tasks were grouped into two factors, one derived from the TRVB, which represented a measure of visual perception, visual memory, and visuo-constructive abilities that saturated the first axis. The second axis was represented by the TRVB and TOLB measurements, which suggested the presence of a second factor that gatheres the ability for visual scanning, complex visual discrimination, and the ability to establish spatial relationships between lines segments by visual confrontation – as measures of visuospatial perception. These results coincide with that indicated in other factorial analyses, which have revealed that TRVB, for example, is based mainly on a visuoperceptual motor factor, and secondarily, on a factor of attention, concentration, and memory.[41] A second factor analysis study found that said test is based on two factors: alertness and psychomotor speed. [42]

In the case of praxis assessment tasks, it was found that two factors explained 62.9% of the total variance, indicating a representative first factor of the functions of simultaneous perception, visuospatial ability, visuo-constructive praxia and non-verbal memory, ability to pay attention to details and ability to organize the perception of complex visual stimuli. In a second factor, the measures of copy time and deferred memory time were grouped.

In relation to the validity of the concurrent criterion, significant correlations were evidenced for the case of the measures included to evaluate praxis, such as TFCRO. This result is consistent with other research indicating that visuomotor skill and memory contribute to performance on tasks with similar cognitive demands.[28] Another study with patients with neurological impairments found that complex figure scores correlated well with other tasks that required viso-constructive and memory skills like TRVB.[23,24]

Concurrent criterion validity was not evidenced for the tasks that assess gnosias, despite the fact that theoretically both groups of tests measure the same construct. In the case of the TDVB, TDOB and TRVB tasks, some subtests of the DNI battery of visuospatial area were used as criterion tasks, among which were the visual perception subtest and the spatial orientation subtest. These criterion tasks share the object of evaluation with the standardized tests, as both groups of tasks evaluate the visuospatial cognitive domain, which include the ability to handle coordinates and spatial syntheses underlying complex constructive activity.[32] This result differs from the ones reported by other researchers who claim high correlations, for example, in the case of the TOLB, when compared to other visuospatial subtests, such as those of the Wechsler Adult Intelligence Scale (WAIS).[27]

Concerning internal consistency for the items of the TDVB, TOLB and TRVB tests, an Omega coefficient of 0.79 was found; while for the praxis coefficients were 0.40 and 0.67, respectively; this indicates barely acceptable consistencies for both cases, and in practical terms allows us to suppose that this group of tasks, although they measure the same constructs,

do not represent homogeneous tasks. It is worth mentioning that some researchers report a Cronbach's alpha of 0.66[43] for the TDVB; Strauss et al. indicate a Cronbach's alpha of 0.60 for TFCRO, 20 values considered relatively low.[44]

Due to the stated above, the Omega coefficient is shown, which, when working with factorial loads, allows to stabilize the calculations and reflect the true level of reliability.[45] These results theoretically agree with those reported by researchers, who consider that a subject's performance on visuospatial tasks depends on the perceptual task, even in the case of apparently related perceptual tasks, for example, subjects who perform well on discrimination tasks and orientation, do not necessarily perform well in movement discrimination.[46] These individual differences in visuospatial and praxical tasks were also reported in another study, in which the visual performance of the subjects showed substantial differences in two perceptual tasks (individuals who performed well in one task did not necessarily obtain good results in another).[47]

Regarding the pretest-posttest reliability, the present results -although they show concordances higher than 60% in most of the evaluated items-, indicate that when analyzing the pValue of the differences between the medians and the correlation coefficients, it is observed that in the assessment of praxis and gnosis, different values are found at both times of application of the tasks, and these are generally not correlated, which allows us to point out that statistically these measures are shown to be unstable over time.

This is consistent with studies that describe low test–retest reliability for visuoperceptual and constructive tasks, such as the one carried out with healthy subjects aged between 17 and 82 years, where the TRVB was applied. In this case, and after an interval of 21 days, the test-retest reliability was 0.57.[48] In another investigation that used a line orientation test and where healthy adults were re-evaluated after one year, a correlation coefficient of 0.59 was found.[49]

The importance of the normative data presented in this research derives from the delimitation of the sample: university students between 16 and 26 years old, with homogeneous sociodemographic characteristics (middle socioeconomic stratum), and at least 12 years old of schooling. The normative data provided differs from other studies in which measures have been standardized to assess praxis and gnosis tasks, especially due to the greater and broader age range used: 18 to 49 years [50] and 18 to 55 years.[51] It is important to point out that a precise age range will improve the reading of the subjects' praxic and gnosis performance characteristics. Some researchers have considered that determining small intervals in age in the standardization of psychometric tests would allow the professional to be aware in advance of a possible cognitive deterioration, in addition to establishing appropriate cut-off points according to age.[52]

Conclusions

Adequate reliability was found related to the application by different evaluators, with the exception of the TRVB, in which the medians show differences, probably attributed to the different forms of the test that can influence its application uniformity. A mean of 34.8 (SD=1.9) was found for the TFCRO, 126.7 (SD=63.5) for the measurement of time in the TFCRO and 28.7 (SD=3.4) for the TDVB. For the TRVB they are discriminated as follows: form "C" 7.9 (1.5), form "D" 7.7 (1.7) and form "E" 8.4 (1.5). In the case of the TOLB, there were differences between men and women: 48.5 (6.9) and 46.1 (8.3), respectively. These differences are consistent with research that found that men perform much better than women on tests of visuospatial skills, especially on the line orientation task.[52]

Adequate content validity was evidenced in all tests; as well as adequate criterion validity of praxis assessment measures, and, low criterion validity, internal consistency and test-retest reliability for the gnosis and praxis tests.

This result is consistent with research that has reported difficulties in the assessment of visuoperceptual and constructional skills, associated with the multifactorial nature of this type of tasks, which require visuospatial, executive and motor skills. Similarly, there are difficulties related to individual variations in the performance of a subject in same tasks according to time intervals, which adds to the wide variety of tests, forms and methods used to measure constructs such as visuo-constructional ability that further complicates the interpretation of the results.

Finally, considering that evaluation instruments have different forms of administration and qualification following diverse adaptations, it is important that neuropsychologists interested in university learning contexts, as well as in the assessment of young university population in clinical contexts, take into account the most appropriate form of administration and scoring for the context in which the test will be applied and, furthermore, consider to the most possible extent the use of standardized instruments in line with the specific culture background of the target population.

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Detection of autism spectrum disorders using the questionnaire M-CHAT R / F: The importance of considering socio-cultural and language aspects

Martí C. Dominique [1] | Aranda Waldo [2] | Eblen-Zajjur Antonio [3]✉

1. Pediatrics Specialization Program, Faculty of Medicine, Diego Portales University, Santiago, Chile
2. Department of Statistics, Diego Portales University, Santiago, Chile
3. Translational Neuroscience Laboratory, Faculty of Medicine, Diego Portales University, Santiago, Chile

Correspondence

Dr. Antonio Eblen-Zajjur
Faculty of Medicine, Diego Portales University, Av. Ejército Libertador 219, Santiago, Chile.

✉ antonio.eblen@udp.cl

Abstract

Introduction: The influence of language and socio-cultural environment on the development of cortical connections is widely acknowledged, as well as the alteration of the latter in contexts of autism spectrum disorders (ASD). The present study evaluated potential differences in the detection of ASD, depending on the language and socio-cultural aspects of the population. Method: A search of publications was carried out in: PubMed, Google Scholar, and Epistemonikos from 2010 to 2020, which validated the use of the M-CHART R/F questionnaire as screening in the early ASD detection in patients between 12 and 36 months of age, without risk factors and in any country in the world. The meta-analysis included three reviewers who evaluated eligibility and extracted the data. The heterogeneity and consistency between studies, as well as the specific differences between each one with the main validation study were evaluated, including, the positivity of the phase 1 and its confirmation in the follow-up of each case. Results: Eight articles met the inclusion criteria; these were carried out in the United States, Argentina, France, Spain, Turkey, Saudi Arabia, Albania and Korea, in their official languages, for a total of 36,842 children. Heterogeneity was low (OR<0.42) for most subsets of the meta-analysis, except for the results obtained in Korea (OR=7.64). There is an association in results between countries (excluding Korea) OR=0.196 [0.178-0.216]; p<10-10. All studies showed significant differences in detection compared to the original validation study. Conclusion: The MCHAT R/F is a valid method for screening for suspected ASD in the general population, but it is dependent of the culture and language of the country.

Keywords: *modified checklist for autism in young children, validation, MCHAT R/F, autism Spectrum Disorders*

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in communication and social interaction in multiple contexts, including deficits in social reciprocity, nonverbal communicative behaviors used in social interaction, and skills to understand, develop, and maintain relationships. Its detection also requires the presence of restrictive or repetitive behavior patterns, interests or activities.[1-12]

Neurophysiological evidence emphasizes the important role of language in the organization of brain networks related not only to language but also to long-term executive control, and the adaptation derived from social diversity in the use of language.[13-16]

The application of techniques such as functional magnetic resonance imaging (fMRI), Magnetoencephalography (MEG) and Electroencephalography (EEG) have made it possible to detect, with various spatial and temporal resolutions, alterations in brain connectivity in patients with ASD, which are considered as potential biological markers for diagnosis.[17-22]

In the case of infants with ASD, in Latin America, clinical guidelines with recommendations for detection and timely intervention are available (Minsal, 2011),[2,23] that propose action plans for the age group between 0 and 4 years and 11 months. The actions included in these guidelines are aimed at the early detection of ASD indicators and their opportune rehabilitation.[2]

Similarly, the American Academy of Pediatrics recommends monitoring and screening for developmental disorders in pediatric consultations for children at 9, 18, 24 and 30 months of age, including early detection of ASD indicators at 18 and 24 months of age,[3,4] which is supported by the fact that ASD diagnosis after 14 months of age can be considered reliable.[5]

The Modified Checklist for Autism in Toddlers, revised with Follow-Up (M-CHAT-R/F)[6] is a 2-stage parent-report screening tool to assess risk for ASD; it is valid for screening children between 16 and 30 months of age, and has simple closed questions (with Yes/No responses). It can be applied by parents, pediatricians, specialists or other health professionals (Stage 1).[6] In cases with scores corresponding to "Moderate Risk", a telephone follow-up is carried out by trained professionals (Stage 2) to obtain more information regarding the questions with "positive" or risk responses. The follow-up interview is designed to clarify and elicit specific examples of typical child behavior, related to each element of the M-CHAT R/F.[24]

The current prevalence of ASD is approximately 1.5% in developed countries; a change in epidemiology has been observed, with an increase in groups that do not present comorbid intellectual disability.[7,12] In addition, there is growing evidence of incidence and prevalence variability of children with ASD in different countries of the world, which could reflect cross-cultural differences in the recognition of indicative symptoms[8] and the possible existence of cultural contrasts regarding eye contact, facial expression and recognition, as well as verbal and non-verbal language, ludic aspects, behavior according to gender, among many other. It should be noted that this happens despite the fact that many countries have adapted the M-CHAT R/F questionnaire to their population, adjusting it to the local cultural context without affecting the original focus of the test.

According to estimates, the number of foreign residents in Chile was around 1.5 million as of December 31, 2019, and had high numbers of non-Spanish speakers; of these, 29,293 corresponded to children between 0 and 4 years of age,[9] which pinpointed the necessity of a health care protocol focused on this pediatric group, as proposed in Vásquez-De Kartzow, 2018.[10]

In accordance with the above-mentioned, this meta-analytical study aims to determine if the MCHAT R/F questionnaire is a valid exploratory method for suspected ASD in general population, regardless of cultural aspects, and if there are significant differences in assessments according to the country or culture of origin.

Multiple evidence strands suggest that language, society and culture shape cortical connectivity, and that autism spectrum disorders (ASD) may be due to alterations in said connectivity. In this regard, the MCHAT R/F used as an initial exploration of ASD has been validated for multiple languages, however, the influence of language and culture on its results has not been evaluated.

Method

A literature review in PubMed, Google Scholar and Epistemonikos — from 2010 to June 2020 — was conducted, for studies that validated the use of M-CHART R/F as a means of exploration in ASD early detection in different

countries. The search terms used were: "Modified Checklist for Autism in Toddlers", "(MCHAT R/F) AND validation", "screening autism", "cross-cultural validation". The selected type of study corresponded to clinical trials and randomized controlled trials. Articles that used the M-CHAT R/F adapted to each country as an exploratory method, regardless of language, were retrieved. Systematic reviews were excluded.

Inclusion criteria: 1) Age of the subject: between 12 and 36 months of age; 2) M-CHAT R/F questionnaire answered by parents in their homes or in primary care centers; 3) Follow-up interview only with parents of children who initially tested positive; 4) Publication date of the article: between 2010 and 2020; 5) In order to include a greater number of countries and cultures, indexation of the publication journal was not considered.

For each keyword the search engine showed a broad match list, of which 35 articles were selected for methodology and results review; in turn, 8 of these articles met the established inclusion criteria and were included in the meta-analysis.[25-32] Table 1 shows exclusion causes.

Table 1. Exclusion causes of 27 of the 35 initially selected studies according to keywords

Total excluded	27
Control cases	6
High risk	5
Missing information	3
Screening comparison	3
Letter to the editor	1
Scale modification	1
Age > 36 months	3
M-CHAT previous version	4
Racial comparison	1

Statistical analysis

Once the studies were selected, their heterogeneity and consistency were reviewed, finding that, with the exception of the case of Korea,[29] results between countries are consistent. Statistical analysis was performed using the STATA program version 17.0.

For each country, it was quantified if a "positive" result on the first stage of the M-CHAT R/F questionnaire had an effect in an also "positive" result in the follow-up application, which suggests a high probability of ASD. A binary measure of association (odds ratio) was used, and it was calculated with a confidence interval of 95%. Additionally, variation coefficients of the various studied groups were compared using the Fligner-Kileen test.

Results

A screening validated in the USA —adapted and translated into different languages (French, Korean, Arabic, Turkish, Albanian, Spanish, etc.) and applied to its population — was compared between culturally different countries,[25-32] to determine if there were significant variances in the "positive" results on stage 2, which indicates a high risk of autism spectrum disorder, and if culture is an influential factor for this outcome.

In the 8 analyzed studies, the M-CHAT R/F questionnaire was administered to a total of 36,842 children, between 12 and 36 months of age and without risk factors; 3,818 of them (8.2%) tested "positive" in stage 1, which warranted follow-up, as indicated by the authors.[6,24] In stage 2, 709 children (1.9% of the total) obtain a "positive" result and were examined with different evaluation scales to diagnose ASD —with the exception of the Korean cases. Approximately 0.62% of this meta-analyzed sample obtained an ASD final diagnosis.

Figure 1 shows that, apart from the study conducted in Korea,[29] there is a significant association in the questionnaire results between the different countries, that showed average values less than 1, with an average OR of 0.196 95% CI [0.178-0.216] ; z: -33.0; $p < 10^{-10}$ (excluding the Korean study). Regarding this OR value, a similar behavior is observed — in a narrow range, and with the lowest values — in the group of studies carried out in the United States, Spain, Turkey and Saudi Arabia. A second group of studies, including the ones performed in Argentina, France and Albania, showed higher OR values than those of the first described group ($p<0.05$; $z=4.52$). Additionally, the dispersions of the OR values evaluated through the coefficients of variation of the first group were statistically lower than those observed in the second group ($p<0.05$; $z=2.37$; Fligner-Kileen test).

In Table 2, the $\chi 2$ analysis performed on the proportions reported in the studies included in this meta-analysis, including or not the Korean study, shows statistically significant values $\chi 2=358.4$; $p=10\text{-}70$ and $\chi 2= 277.7$; $p=10\text{-}250$, respectively, and expresses the differences between the proportions found for each country and language.

Figure 1. Forest Plot of the meta-analysis of studies in different countries and languages in which the MCHAT R and R/F was applied to the general population in children aged 12 to 36 months without risk factors

	MCHAT-R		MCHAT-R/F			
	+	n	+	n	OR (95%IC)	OR (95%IC)
Argentina	18	420	2	16	0,34 (0,07-3,26)	
USA	1155	16115	348	807	0,13 (0,12-0,15)	
France	108	1250	20	88	0,31 (0,18-0,56)	
Spain	158	6625	32	126	0,06 (0,04-0,10)	
Turkey	658	6712	221	437	0,17 (0,14-0,21)	
Saudi Arabia	127	1078	46	81	0,12 (0,07-0,19)	
Albania	253	2594	26	227	0,42 (0,26-0,69)	
Meta-Analysis	2477	34794	695	1782	0,20 (0,18-0,22)	
Korea*	541	2048	14	541	7,64 (0,43-14,3)	

*The study by Seung et al. 201529 in Korea was excluded after heterogeneity testing.

Table 2. Positivity proportions when applying MCHAT R/F stage 1 in each language/country and their statistical comparison with the validation study in English (USA).

Language (Country)	% MCHAT	n	IC 95%	z	p
English (EEUU)	7.16	16115	7,08-10,2		
Spanish (Argentina)*	4.30	420	2,56-6,69	-2,27	0,02
French (France)	8,64	1250	7,14-10,34	2,03	0,04
Spanish (Spain)*	2,38	6625	2,03-2,78	-15,1	10^{-50}
Turkish (Turkey)	9,80	6712	9,10-10,54	8,39	10^{-17}
Arab (Saudi Arabia)	10,70	1188	8,99-12,59	4,73	10^{-6}
Albania (Albanian)	9,75	2594	8,64-10,96	5.12	10^{-7}
Korea (Korean)	26,4	2048	24,52-28,38	33.77	10^{-200}

*The proportions reported in the two studies carried out in Spanish-speaking countries (Spain and Argentina) showed highly significant statistical differences, with the proportion reported in Argentina being higher ($z = 5.7$; $p = 10^{-8}$).

Discussion

In the present meta-analytical study, the influence of language and socio-culture on ASD prevalence reports obtained by applying the MCHAT R/F in general populations aged 12 to 36 months without risk factors was evaluated. Despite extensive validation of the M-CHAT R/F scale in each of these languages and cultures,[25-32] phase 1 prevalence for ASD was statistically different for each language/country. These contrasts were also found in cases from the same language, in studies reported for Spain and Argentina (Spanish), and between Romance languages, in the case of Spanish (Spain and Argentina) and French (France); which suggests little influence both of the linguistic root, in the case of Romance languages, and of the language itself, in the case of Peninsular Spanish in relation to Argentinian Spanish. These results lead us to attribute the differences reported between the meta-analyzed studies of Spanish-speaking countries, not only to the language but also to other socio-cultural factors, such as familiar, social, as well as customary, and other individual and collective behaviors, all in a comprehensive context of high impact and transcendence in cerebral cortical connectivity and execution.[13-17,33-35]

The extensive application and exhaustive validation of the MCHAT R/F for each language,[25-32] support the idea that the instrument is capable of detecting cases of ASD in initial examinations for subsequent confirmatory evaluation,[6] however, the results of the present study suggest the existence of differences between studies associated with language and/or particular socio-cultural factors. It is very likely that other aspects are also involved in the generation of these contrasts, nevertheless, the predominance of communication and expression factors and their high association with socio-cultural features indicate its predominant role in the explanation of the differences found.

It is well known how language and society – understanding the latter as cultural integrality – shape neurodevelopment and, specifically, cortical neuronal connectivity in health[13-17,33] and cognitive disorders in general,[17-22,33-35] as well as in ASD.[21,38] This study results reveal the impact and contribution of language and/or socio-cultural features in the different levels of exploratory detection of ASD when applying the MCHAT R/F, and highlight the need for values of reference specific to each society, culture and/or language, since these aspects, despite sharing many elements in common, differentially shape cortical connectivity.

The authors of the study carried out in Korea, which turned out to have significant differences with respect to the other studies, considered that, despite the validation of the MCHAT R/F in the Korean language,[29] certain questions may not be well understood by the parents, which could be related to their own cultural dynamics; for example, when making unusual finger movements near their eyes, many answered "yes", since such gestures are common in Korean games. Another example is the case of the Arab culture, in which it is customary to look down or simply avoid direct eye contact in first encounters or when one person is of higher rank, analogously, it is impolite to keep your eyes fixed on who is speaking or to point with a single finger.[30,36]

In turn, Zachor et al.[37] compared the comorbidity associated with ASD in children from the USA, Israel, South Korea and England, concluding that avoidance behaviors are probably more acceptable in South Korean children and, therefore, they are not reported as "present"; while in the US and England these behaviors are significant, although no mayor differences were reported regarding comorbidities between these countries.

It is worth mentioning the case of a cohort of 2,459 children obtained throughout North America, to which the ADOS (Autism Diagnostic Observation Schedule) test was applied,[8] in order to analyze the potential bias in the variability of social and communication behaviors according to race, ethnicity or gender. This study found that unusual eye contact, use of stereotyped phrases, and immediate echolalia were higher in black children compared to white children.

According to the above-mentioned, the importance of considering the intercultural variations associated with socialization and language when making impressions and/or clinical diagnoses of developmental disorders is confirmed.

Although there is currently a growing prevalence of ASD diagnoses – largely attributable to the dissemination and application of evaluation strategies, broader diagnostic criteria and greater awareness of this condition by health professionals and families –, it is necessary, now more than ever, to understand the influence of language and/or socio-cultural factors on cortical connectivity and its impact on our evaluation and detection instruments, in order to avoid alpha and beta diagnostic errors for different societies and the patients that originate from them, and taking into account the dynamic plasticity of brain connectivity in neurodevelopment.

It should be noted that, as with most behaviorally defined disorders, the point at which normal variation converges with disorder is an arbitrary decision, and is likely to be influenced by cultural values and expectations, since this shapes behavior and the standards of what is or is not acceptable.[38]

We must then consider the differences that exist between each culture, socially accepted behaviors, verbal - non-verbal language, as well as the predominant game dynamics, when applying these tests. Thus, overdiagnosis will be avoided, all this in consideration of the emotional, social and legal implications it has for the child and his family.[39]

Concluding Remarks

• The MCHAT R/F questionnaire is a valid screening method for suspected ASD in general population, but it is dependent on cultural traits.
• The main difficulty in combining the results of a screening method validated for different languages and countries relates to the diverse nature of the participants, the culture of each one, and the parental understanding of children's behavior (appropriate/inappropriate).
• The existence of differences among MCHAT R/F detection percentages between different countries and the original validation study carried out in the USA was determined.
• The point at which normal variation converges on disorder is an arbitrary decision and is influenced by cultural values and expectations.
• The application of the MCHAT R/F requires considering differences that exist in each culture, socially accepted behaviors, verbal - non-verbal language, and significant game dynamics.

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Description of the referral centers for patients with epilepsy for the implementation of the TeleECHO project in a national institute of health

Santos-Peyret Andrea S.[1] | Crail-Meléndez Daniel[2] | Sebastián-Díaz Mario A.[3] | Velasco-Vázquez Carmen[4]
Del Río-Quiñones Manuel Alejandro[5] | Gómez-Figueroa Enrique[6] | Reséndiz-Aparicio Juan Carlos[7]
Rubio-Donnadieu Francisco[7] | Martínez-Juárez Iris E.[1,8]✉

1*.Epilepsy Clinic
2*.Department of Neuropsychiatry
3*.Health Sciences Doctorate Program, Anáhuac University, North Campus, State of Mexico, Mexico
4*.External Consultation
5*.Subdirectorate of External Consultation
6.National Institute of Neurology and Neurosurgery Manuel Velasco Suarez, Mexico City, Mexico
7*.Epilepsy Priority Program
8*.Cognitive and Clinical Neurophysiology Laboratory.

*National Institute of Neurology and Neurosurgery Manuel Velasco Suarez, Mexico City, Mexico

Correspondence

Dr. Iris E Martínez-Juárez
Epilepsy Priority Program. National Institute of Neurology and Neurosurgery Manuel Velasco Suárez. Insurgentes sur 3877, Col. La Fama, Tlalpan, C.P. 14269, Mexico City, Mexico.

✉ clinicadeepilepsia@innn.edu.mx

Abstract

Background: Epilepsy is defined as a neuronal predisposition to generate epileptic seizures; all diagnosed patients must follow the guidelines of the clinical record and have a reference and counter-reference system.
Objective: To describe the care centers and characteristics of patients with epilepsy referred to the Comprehensive Epilepsy Care Center 1 (CAIE 1, by its acronym in Spanish) of the National Institute of Neurology and Neurosurgery (INNN, by its acronym in Spanish), as well as evidencing the need for the decentralization of these processes through new technologies and projects such as TeleECHO.
Material and methods. An observational, descriptive and cross-sectional study was carried out. Information was obtained through outpatient referral sheets, in order to review the centers, levels of care, place of origin, and reason for the referral of patients with epilepsy to the CAIE 1, from January to December 2017. Patient information sheets without complete data were excluded.
Results. Out of 4,866 patients referred to the INNN, 627 patients had epilepsy (mean age of 33.34 ± 15.33 years, 52.8% were women). Most of the referred patients came from private physicians, and primary and tertiary care centers in the Megalopolis (Mexico City, State of Mexico, Hidalgo, Morelos, Querétaro and Tlaxcala).
Conclusions. The study allowed us to know and describe the health care centers that refer patients with epilepsy to the CAIE 1 of the INNN in one year. This knowledge will serve to implement the ECHO project, which seeks to improve the referral and counter-referral system and decentralize the care offer for patients with epilepsy. The implementation of said telemedicine program in national centers of most referral aims to reduce the epilepsy treatment gap in Mexico.

Key words: *epilepsy, referral, telemedicine, information technology*

Introduction

Epilepsy is a brain disease characterized by a neuronal predisposition to generate epileptic seizures.[1] In Mexico, the estimated prevalence of epilepsy is situated between 10 and 20 per 1,000 people;[2] all treated patients medical history must follow the guidelines regarding clinical records management [4] and, ideally, have a referral and counter-referral system.[5] There are multiple factors that can affect epilepsy care: the cost of antiepileptic drugs, their limited availability, the socioeconomic level of the patients, the disparity between health centers in the private and public sectors, the shortage of neurologists and epileptologists, as well as the access limitations in certain social sectors to medical care and diagnostic methods, among others.[2] In this regard, the Epilepsy Priority Program (PPE, by its acronym in Spanish) of the health sector in Mexico, has as its objective to regulate, coordinate and optimize strategies and actions in favor of patients with epilepsy, their families and society. The PPE focuses on two lines of work: the development of care centers and the strengthening of primary care.[3] In 2020, the PPE registered 82 comprehensive care centers for epilepsy in public hospitals across the health sector. Among them was the Manuel Velasco Suárez National Institute of Neurology and Neurosurgery (INNN), a highly specialized neurological center in Mexico City, where the Comprehensive Epilepsy Care Center 1 (CAIE 1) is located.

The criteria for admission and permanence at CAIE 1 of the INNN are: to be a patient referred from a secondary care with drug-resistant and/or uncontrolled epilepsy; to be a candidate for epilepsy surgery; or to be a patient of an institution with an agreement to be treated at the INNN (Source: Official letter of criteria for admission and permanence at the INNN Epilepsy Clinic).

In 2017, the INNN provided 2,051 consultations for patients with first-time and subsequent epilepsy and, during 2018, 1,680 (Source: INNN Clinical File). These figures show the need for the decentralization of health services, as promoted by the General Health Law.[4]

Objective

To describe the source center and the characteristics of the referral of patients with epilepsy sent to the Comprehensive Epilepsy Care Center 1 (CAIE 1) of the National Institute of Neurology and Neurosurgery (INNN), in order to demonstrate the need for decentralization of care with new technologies and through projects such as TeleECHO.

Materials

The outpatient referral forms of all patients referred to epilepsy consultation to the CAIE 1 of the INNN in the period from January to December 2017 were considered, forms without complete data were excluded. A database was created expressly in the Excel program for subsequent analysis using descriptive statistics with measures of central tendency and proportions, depending on whether they were dimensional or nominal variables, respectively. To analyze the information of the referred patients, the following data was taken into account: the reasons for referral to said institution, the sex of the patients, the doctors who referred, as well as the centers and states from which the referrals came. The study was approved by the Ethics and Research Committees of the INNN (project No. 40/19).

Health centers and clinics with family or general practitioners were considered as primary care; hospitals that have basic specialties as Internal Medicine, Pediatrics, Gynecology, General Surgery and Psychiatry were included as secondary care, and, finally, highly specialized health institutions that have advanced diagnostic equipment for the treatment of complex diseases were considered as tertiary care.[5]

Methods

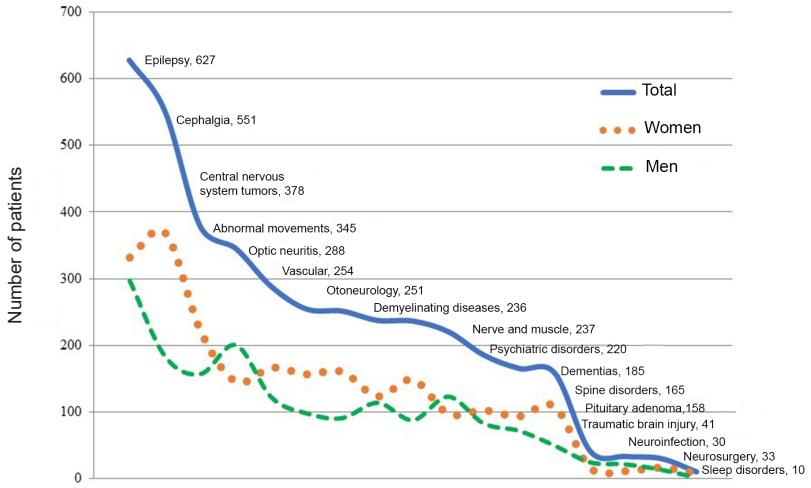
An observational, descriptive, cross-sectional and prospective study was carried out.

Results

In the period from January to December 2017, a total of 4,866 patients were referred to the INNN. Eight hundred fifty-seven patient's referral forms (17.6%) had a diagnosis of "assessment" without any specification of the neurological pathology for which they were referred. Four thousand nine patients (82.4%) were referred for various neurological pathologies. The three main reasons were: epilepsy, headache, and tumors of the central nervous system (Figure 1).

A total of 627 patients with epilepsy were referred to the CAIE 1 at the INNN. Three hundred thirty-one of them were women (52.8%) and 296 (47.2%) were men. The mean age at the time of referral was 33.34 ± 15.33 years (range 15 to 88 years). According to the distribution by age of the patients, in both sexes the age group of 15 to 20 years

Figure 1. Causes for the referral of patients to the INNN "MVS", total and divided by sex

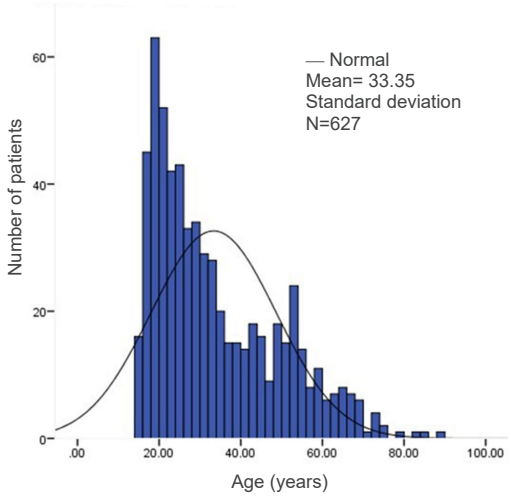


INNN "MVS"= National Institute of Neurology and Neurosurgery "Manuel Velasco Suárez"

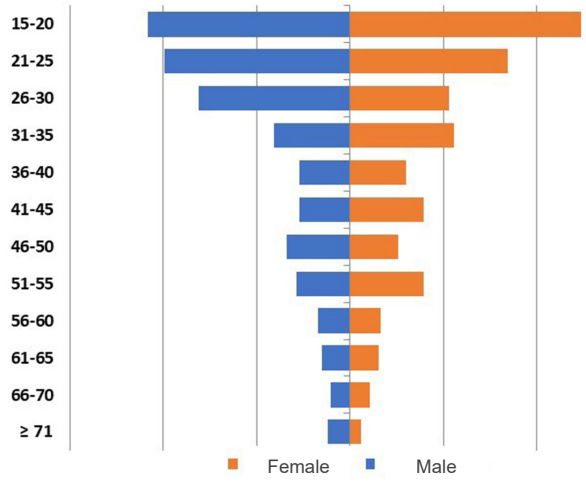
prevailed with 146 patients, equivalent to 23% (n=146) of total referrals, with 56% of women (82 /146) (Figure 2). 29% (182/627) of patients were referred by a private physician, the rest, by public sector physicians. According to the level of healthcare, 32% of patients (201/627) were referred from primary care, 8.6% (54/627) from secondary and 28.3% (178/627) from tertiary; only 1.89% (12/627) were referred from other units (Table I).

Figure 2. Distribution by age and sex of epilepsy patients referred to the CAIE 1 of the INNN "MVS"

A.Distribution of patients referred to the CAIE 1 of the INNN "MVS" by age



B. Age groups of patients referred to the CAIE 1 of the INNN "MVS" by sex



CAIE 1= Comprehensive Epilepsy Care Center 1, INNN "MVS" = National Institute of Neurology and Neurosurgery "Manuel Velasco Suárez"

Table I. Referral centers of epilepsy patients to the Comprehensive Epilepsy Care Center 1 of the National Institute of Neurology and Neurosurgery "Manuel Velasco Suárez"

Referral centers	Number of patients (%)
Primary care	201 (28%)
Secondary care	54 (9%)
Tertiary care	178 (32%)
Private physicians	182 (29%)
Others	12 (2%)
Total	627 (100%)

The states that reported the highest number of referred patients were Mexico City, with 60% (376/627), and the State of Mexico, with 27.9% (175/627), followed by other states of the Megalopolis (Table 2).

Table 2. States that referred epilepsy patients to the Comprehensive Epilepsy Care Center 1 of the National Institute of Neurology and Neurosurgery "Manuel Velasco Suárez"

States	Number of patients n (%)
Mexico City	376(60%)
Estate of Mexico	175 (27.9%)
Hidalgo	13 (2%)
Morelos	12 (1.9%)
Oaxaca	10 (1.59%)
Puebla	9 (1.43%)
Guerrero	8 (1.27%)
Michoacán	8(1.27%)
Chiapas	5 (0.79%)
Veracruz	5 (0.79%)
Guanajuato	2 (0.31%)
San Luis Potosi	1 (0.15%)
Tabasco	1 (0.15%)
Tlaxcala	1 (0.15%)
Yucatan	1 (0.15%)
Total	**627 (100%)**

Discussion

During the examined year, epilepsy was the main reason of referral to the INNN —only after non-specific neurological assessment—, in addition to being the principal cause for outpatient care at said institution. Most of the patients with epilepsy were referred from primary and tertiary care units, as well as physicians from the private sector.

A large part of the patients is referred from Mexico City and the State of Mexico, as well as from cities in the Megalopolis; this is probably due to the proximity and adequate access to health referral systems at the local level.

In states further away from Mexico City, we observe a limitation in terms of referral, probably caused by the scarcity of resources of the patients to travel to said institute, or because some of these states have highly specialized hospitals that provide care to these patients.

Population-based studies of epilepsy incidence report a bimodal distribution of the disease, with peaks between 5 to 9 years of age and over 64 years of age,[6] although the prevalence of the disease can be at any age. In this investigation, referral predominated in the age group of 15 to 20 years of age, followed by the group of 21 to 30 years, who are economically active population. On the other hand, in the distribution according to sex, predominance of the referral of female patients is observed — it is well-known that the prevalence of epilepsy is also higher in females in the group of 15 to 20 years of age, and that it increases in age groups older than 64 years.[7]

Regarding this, the new Mexican healthcare model — introduced in 2015 by the Ministry of Health — stablishes strategies for the implementation of health rights, whose main objective is to achieve high levels of coverage, nevertheless these efforts have not been sufficient. In the case of epilepsy patients, there is currently a high demand of tertiary care, however the majority of these patients, instead of being referred from primary and secondary care and public hospitals, are sent from tertiary care and private physicians.[8] One of the possible reasons for the higher referral from tertiary care is that patients who were diagnosed with epilepsy in pediatric age are sent from tertiary care centers of neuropediatrics to adult neurology to the CAIE 1 of the INNN; another explanation could be that patients referred to local tertiary care centers are redirected from these institutions to the CAIE, this in addition to the fact that there are tertiary care hospitals that do not

have epilepsy surgery programs, and therefore refer patients to the CAIE 1. These, among many other reasons, seem to explain the increase in tertiary-to-tertiary care referral. It is noteworthy that this high referral of patients from tertiary care hospitals ultimately generates a failure in the referral system and produces a "boomerang" effect, in which the patient experiences an increasing gap to access timely diagnosis, treatment and follow-up.

When contrasted with those of high-income countries —where 30 to 50 per 100,000 new cases of people with epilepsy are registered per year —, it is worth mentioning that these figures can be twice as high in low-income countries. Furthermore, it has been documented that the number of neurologists in the latter is even lower:[9] in low-income countries there are a median number of neurologists of 0.1 per 100,000 population, compared to 7.1 per 100,000 population in high-income countries. On the other hand, in the Mexican case, the frequency of drug resistance in the INNN has been reported in up to 56% of patients.[10]

Based on international statistics, it is observed that approximately 70% of people with epilepsy are controlled with antiepileptic drugs; and that 30% have inadequate seizure control, even with correct drug therapy.[11] It should be noted that 73.3% of patients with active epilepsy who reside in rural areas of low- and middle-income countries do not receive treatment or receive it inadequately; which is known as epilepsy treatment gap.[12]

According to these data, most epilepsy patients in Mexico could be treated at a primary or secondary care center. According to the CENETEC Clinical practice guide for epilepsy patient care,[12] the criteria for the referral of a patient to a tertiary care center are: having uncontrolled epilepsy after a treatment with antiepileptic drugs of approximate 2 years without achieving effective control, inadequate control despite appropriate doses within the tolerance limit, if the patient is at great risk of experiencing adverse effects from treatment, existence of structural lesion, presence of psychiatric or psychological comorbidity, existence of diagnostic doubt, and presence of cognitive or behavioral impairment, among others.

The referral and counter-referral system constitutes a medical administrative procedure —performed by the health personnel — carried out between operating units of the three levels of care, that enables the referral-receiving-returning of patients, and that has the purpose of providing timely, comprehensive and adequate medical care.[13]

The Procedure manual for the referral and counter-referral of affiliates or users offers guidelines for the process that the patient must follow to access medical examination, and establishes that this procedure must be comprehensive and involve a large group of health workers, including social workers, nurses and physicians; this in order to produce an adequate referral system for patients, which refers them to the level of care they require according to their condition for prompt diagnosis and correct treatment.[14]

It is therefore imperative the enhancement of the referral-counter-referral system at the tertiary care of the CAIE 1 at the INNN, following the guidelines provided in the Procedure manual and considering the data presented in this study.

A general overview of the referral and counter-referral of patients with epilepsy to the CAIE of the INNN will allow us to implement international systems, such as the ECHO Project (Extension for Community Healthcare Outcomes), which is dedicated to attend vulnerable populations by providing telementoring. TeleECHO is conformed by multidisciplinary teams, which share their knowledge with primary care physicians that are in constant contact with epilepsy patients; these strategies can help provide greater access to patient care, avoid delays, and decentralize tertiary care services.[15]

Conclusions

This study allowed us to identify and describe the health care centers that refer epilepsy patients to the CAIE 1 of the INNN in one year. This knowledge seeks to improve the referral-counter-referral system and decentralize healthcare for patients with epilepsy. One of the proposed actions is to reevaluate the referral to CAIE 1 of private physicians, and another to channel patients to their corresponding primary, secondary or tertiary care centers according the federal entity — as in other Latin American countries referral systems —[6] through inter-institutional agreements, especially between tertiary care hospitals and the current 82 PPE centers.

Finally, with this study, we strive for the implementation of future telemedicine strategies[16] and TeleECHO in the centers with the highest referral of patients to the CAIE 1 of the INNN, which can lead to the decrease of the epilepsy treatment gap in Mexico.

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Fabry Disease and Cerebrovascular Disease

Pérez-Jovel Enrique [1,2] | Cano-Nigenda Vanessa [1]✉ | Manrique-Otero Diana[1] | Castellanos-Pedroza Enrique[1] | Aguilar-Parra Lilia Georgina [1] | Galnares-Olalde Javier Andrés [1] | Arauz Antonio [1]

1. Cerebrovascular Disease Clinic, National Institute of Neurology and Neurosurgery "Manuel Velasco Suárez", Mexico City, Mexico
2. Neurology Service, Salvadoran Social Security Institute (ISSS), San Salvador, El Salvador

Correspondence

Dr. Vanessa Cano Nigenda
Cerebrovascular Disease Clinic, National Institute of Neurology and Neurosurgery Manuel Velasco Suárez, Insurgentes Sur 3877, Col. La Fama, Tlalpan, Mexico City, Mexico.

✉ v.canonigenda@gmail.com

Abstract

Fabry Disease (FD) is a genetic pathology related to the X chromosome (manifested predominantly in carrying men and women) caused by deficit of alpha α-galactosidase A enzyme (also known as ceramide trihexoside), that catalyzes the hydrolytic cleavage of the terminal molecule of galactose from Gb3 (globotriaosylceramide). FD presents phenotypically with inadequate glycosphingolipids metabolism, which affects cell membranes leading to multisystemic clinical manifestations. In addition to cerebrovascular disease (CVD), that mainly affects young patients, other frequent complications are renal, cardiac and dermatological. Due to its low prevalence, chronic and non-specific evolution, with manifestations in young adult life, it is difficult to identify it. Its diagnostic confirmation requires measurement of the activity of the enzyme α-galactosidase A, accumulation of globotriaosylceramide (Gb3), and/or genetic determination by mutation of the GLA gene (gene for galactosidase Xq22.1). At the moment, there is no specific treatment for FD, only symptomatic treatment for the sequelae it generates on a systemic level. The objective of this study is to offer a general overview of the epidemiologic, fisiopathologic and clinic aspects of the FD, with special interest in its manifestation as cerebrovascular disease (CVD), for differential diagnosis consideration.

Keywords: *Fabry disease, cerebrovascular disease*

Background

Fabry Disease (FD) was initially recognized under the name of "hemorrhagic papular purpura",[1] when dermatologists Johannes Fabry and William Anderson first described angiokeratoma corporis diffusum in 1898.[2] Initially it was documented as a systemic vascular disease, and later on as a lipid storage disorder.[3,4] Accumulation of the glycolipids ceramide trihexoside (now called globotriaosylceramide (Gb3 or GL-3)) and galabiosylceramide in a variety of different cell types was identified in 1963;[5] several years later, the defect was established as insufficient activity of the ceramide trihexosidase enzyme, that catalyzes the hydrolytic cleavage of the terminal galactose molecule of Gb3.[6] The X-linked nature of the disease was first recognized in 1965.[7]

Definition

FD (OMIM #301500),[8] or *angiokeratoma corporis diffusum*, is a rare and highly debilitating inherited disorder of glycosphingolipid metabolism, associated with renal, cardiac, and cerebrovascular complications.[9]

Deficiency of agalactosidase, a lysosomal hydrolase, leads to progressive accumulation of glycosphingolipids (primarily ceramide trihexoside (GL-3 or Gb3)) in most visceral tissues, including vascular cells (endothelial and smooth muscle cells), heart cells (cardiomyocytes and valve cells), kidney cells (tubular and glomerular cells), nerve cells and mainly in the lysosomes of the vascular endothelium. The progressive accumulation of endothelial glycosphingolipids produces

tissue ischemia and infarction and leads to the principal clinical manifestations of the disease.[10]

Epidemiology

The prevalence of FD has been estimated to be around 1 in 40,000 males.[11] Another study found 12 of 37,104 consecutive male neonates with specific mutations in the α-galactosidase A gene (X-linked Xq22.1, as will be described in Physiopathology);[12] in turn, Clarke estimated in 2007 1 patient with FD for every 55,000 male births.[13]

Cerebrovascular manifestations are frequent both in the homozygous group and the symptomatic heterozygous. More importantly, these manifestations may be the first indication of the disease.[10] In a prospective study of 721 patients aged 18 to 55 years, 4.9% of male patients and 2.4% of female patients had biologically significant mutations in the GLA gene.[14]

In Mexico there are no studies on FD prevalence or its neurological manifestations, probably due to its low incidence and the diagnostic difficulty that it implied until a few years ago. In general, FD and its manifestation as Cerebrovascular Disease (CVD) are concealed under the classification of cryptogenic etiology, a common final diagnosis of CVD. In relation to this, it is worth mentioning the study by Barinagarrementeria et al., who collected a sample of 300 patients aged under 40 years with ischemic CVD in its different varieties, of which 32% were classified as cryptogenic, that is, without achieving the identification of the specific etiology;[15] it is likely that some of these cases could correspond to FD, however, this disease was not discarded.

In Argentina, a multicentric study carried out in 2017 collected data from 311 patients with CVD (80% infarctions, 9% transient ischemic attacks (TIAs) and 11% intracerebral hemorrhages), of which only 1 case presented evident FD with a pathogenic mutation: c.888G> A/p. Met296Ile/Exon 6, representing 0.3% of the sample and 1% of the patients with cryptogenic cerebral infarcts.[16]

In 2017, the Canadian Fabry Stroke Screening Initiative Study Group identified a single case with a genetic variant of uncertain significance (p.R118C) and no well-recognized pathogenic variants from a cohort of 365 patients with cerebral infarction and 32 with TIA, between 18 and 55 years of age. As a result, if such variant is considered pathogenic, FD prevalence would be of 0.3%.[17] This suggests that, in this population, more cost-effective methods for diagnosing FD should be applied instead of systematic genetic screening.

Pathophysiology

FD is considered an X-linked disorder (Xq22.1), mutating the GLA gene that encodes the α-galactosidase A protein (GLA, 300644),[8] with a high degree of penetrance in men, and intermediate in women: about 50-70% of women with mutations in the gene have manifestations of FD, while almost 100% of men have disease complications.[10] The α-galactosidase A gene is 12kb long, with seven exons and encodes a 429 amino acid precursor protein which is processed to a 370 amino acid glycoprotein that functions as a homodimer. There are 596 known mutations described for this gene, of which 416 are nonsense/stop mutations, 83 small deletions, 19 large deletions, 32 splice defects, three complex rearrangements, and one large insertion.[7]

The primary disease process begins in infancy, or even in fetal development stage, however, unlike many other lysosomal storage diseases, most patients remain clinically asymptomatic during the first years of life. In FD, lysosomal storage and deficient α-galactosidase A activity in plasma and leukocytes are thought to generate globotriaosylceramide accumulation and glycosphingolipids with cellular dysfunction, triggering a cascade of events that include cell death, compromised energy metabolism, small vessel injury, dysfunction of potassium-activated channels in endothelial cells, oxidative stress, impaired autophagosome maturation, and tissue ischemia, which can result in progressive organ dysfunction.[18]

Clinical manifestations (Table 1)

1.- Initial clinical manifestations

The most common initial symptoms of FD are episodic pain crisis that last from minutes to hours, primarily affecting the feet or hands, usually precipitated by exercise, fever, or heat, and modified by acetaminophen.[19] Mechanisms responsible for producing such crisis are not well known, but it is possible that glycophospholipids storage within the endothelial cells of the vasa nervorum, perineural cells, or dorsal root and autonomic ganglia, may cause altered vasomotor reactivity, resulting in a hypoxic state.[11]

Table 1. Clinical features in patients with Fabry disease. Modified from Germain D

System	Signs and symptoms
Sensory organs	– Ocular Cornea verticillata Posterior cataract Vasculopathy (retinal, conjunctival) – Auditory (vertigo/tinnitus) Sensorineural hearing loss
Central Nervous	– Cognitive impairment – Headache – Hemorrhagic or ischemic stroke with posterior circulation predominance – Psychiatric disorders
Peripheral Nervous	– Painful neuropathy (predominantly small fiber) – Neuropathic pain (Acroparesthesias) – Dysautonomia – Intolerance to heat or cold – Hypohidrosis or anhidrosis
Cardiovascular	– Arrhythmia – Unexplained ventricular hypertrophy – Conduction disorders on the electrocardiogram – Valvular heart disease
Respiratory	– Asthma – Dyspnea due to reduced exercise capacity
Digestive	– Postprandial abdominal pain – Nausea/vomiting – Episodic diarrhea – Early satiety
Nephron-urinary	– Microalbuminuria/proteinuria – Hematuria – Nephrotic syndrome – Kidney disease of undetermined etiology
Skin	– Angiokeratomas – Dyshidrosis (hypo/anhidrosis)

2.- Classic clinical manifestations

Patients with the classic form of the disease (no residual α-galactosidase A activity) have typical dysmorphic abnormalities, particularly on the face. These dysmorphisms include periorbital fullness, prominent supraorbital ridges, bushy eyebrows, receding forehead, prominent earlobes or ear rotation, pronounced nasal angle, large nose/bulbous nasal tip, prominent nasal bridge, wide alar base, full lips, coarse facial features, and prognathism.[7] During adolescence, skin lesions (angiokeratomas) appear, which are usually located at the periumbilical, genital and thigh root levels.[20] The accumulation of cytoplasmic material with a lipoid appearance causes epithelial deformation of the glomerular tufts, of the tubules, glomerular endocapillary cells, arteriolar muscle cells, that clinically manifest as proteinuria and renal failure.[8] The latter is the primary cause of death in patients with FD.[21]

3.- Manifestations of FD in the nervous system.

FD neurological complications are common and affect both the central nervous system (CNS) and the peripheral nervous system (PNS).[10] Data from the international Fabry Registry, a large cohort of 2,446 patients, indicate that CVD events are frequent in homozygotes and heterozygotes, occurring in 6.9% and 4.3%, respectively;[22] of which 87% were ischemic and 13% were hemorrhagic.[23] In Fabry Registry, the majority of patients experienced a first stroke between the ages of 20 and 50, and 22% had a first stroke before the age of 30.[24] CNS manifestations of FD include: cerebrovascular disease, hearing impairment with tinnitus, vertigo, psychiatric disorders, and cognitive impairment.[10]

3.1.- Clinical manifestations of FD as cerebrovascular disease

Homozygous men may present with dysarthria, diplopia, vertigo, nystagmus, nausea and/or vomiting, hemiparesis, ataxia, or hemibody sensory symptoms, related to the location and type of CVD that they develop. Headache is quite uncommon, reported in only 20% of patients. In most patients (58%), presentation is compatible with ischemia of vertebrobasilar territory, while anterior circulation was positively symptomatic in approximately 20% of patients.[25]

Vascular dementia due to penetrating small-vessel disease has also been described in patients with FD and should be considered in the evaluation of unexplained dementia, particularly in men younger than 65 years.[26,27]

Heterozygous females may also develop symptoms of neurological impairment, the most reported being cognitive impairment, vertigo, ataxia, hemiparesis, hemibody sensory

symptoms, and headache. In half of the patients, the clinical presentation was consistent with involvement within the vertebrobasilar territory, while the carotid territory was definitely affected in only 10% of cases.[25] Central retinal artery occlusions have also been reported[28] as well as central retinal vein occlusions.[29] In addition to dolichoectasia, white matter lesions and the "pulvinar sign", characterized by hyperintensity in the posterior region of the thalamus, can be observed in the T1 sequence of the MRI.[9]

Common features in the PNS include: peripheral neuropathy (particularly small-fiber neuropathy) with acroparesthesias, autonomic dysfunction characterized by hypohidrosis, intestinal dysmotility, and peripheral thermal and vasomotor dysregulation.[10]

3.2.- Pathological findings in the nervous system
Neuropathologic autopsy findings are consistent with prior events of cerebral ischemia and, rarely, intracerebral hemorrhage; extensive and superficial hemispheric infarcts, multiple small and deep infarcts and infarcts of the brainstem and/or cerebellum can also be observed, the latter being more frequent in symptomatic homozygotes and heterozygotes.[25]

The vessels of the circle of Willis often appear thickened. The narrowing of the lumen and intracellular deposits in arteries and arterioles are additional discoveries.[19] Dolichoectasia of the basilar and vertebral arteries, and less frequently of the carotid arteries, is a constant finding in both homozygotes and symptomatic heterozygotes.[25]

Ischemic and hemorrhagic CVD in FD seem to occur in a proportion similar to that observed in general population, however, at a younger age, TIAs seem to be a risk factor for CVD. Hypertension has been considered the most important risk factor for CVD in FD, and its effect is probably potentiated by underlying vascular degeneration secondary to glycosphingolipid deposits. In the Fabry Registry, patients with CVD were more likely to report a history of hypertension compared with FD patients without CVD, 52.9% *vs*. 20.5%, respectively.[9]

Various cerebral blood flow and intracranial vessel walls abnormalities have been identified, which may not be exclusive to the arterial system. Several mechanisms can contribute to FD vasculopathy, including: endothelial dysfunction, dysregulation of nitric oxide pathways, prothrombotic state, hyperhomocysteinemia, elevated levels of lipids and leukocyte adhesion molecules (Table 2).[19]

The dolichoectasia frequently found in FD, particularly in the large vessels of the posterior circulation, may be related to mechanical weakening of the vessel wall, caused by glycosphingolipid deposits and hypertension. Pathophysiologic mechanisms of CVD associated with dolichoectasia include embolus formation and occlusion of penetrating brainstem arteries. Cardiac involvement in FD can also predispose to CVD, mainly its association with arrhythmias.[9]

Table 2. Mechanisms of cerebral infarction in Fabry disease. Modified from Caplan, et al.

1. Intrinsic vascular pathology
a. Complete or partial thrombosis of main arterial trunks
b. Stretching, distortion and obstruction of tributary vessels
c. Artery-to-artery embolism
2.Glycosphingolipid deposition in the vessel wall with secondary occlusion
3. Cardioembolism
a. Septal motion abnormalities secondary to ischemic heart disease
b. Valvulopathies
c. Hypertrophic cardiomyopathy
4. Altered autonomic function
a. Arterial hypertension
b. Arterial hypotension
5. Prothrombotic states
a. Platelet activation
b. Activation of endothelial factors

Diagnosis (Figure 1)

In men, the diagnosis of FD is made by measuring the activity of the enzyme α-galactosidase A in plasma or peripheral leukocytes. On the contrary, women with suspected FD due to heterogocity may have normal levels of α-galactosidase A activity, so this measurement is not useful, and they must undergo GLA genotyping. Elevated levels of α-galactosidase A substrates in plasma and urine (Gb3 and lyso-Gb3) suggest FD diagnosis.[30]

The blood sample required for this diagnosis is 3ml of whole blood collected in a tube with ethylenediaminetetraacetic acid (EDTA). Currently there also exists enzymatic diagnosis in dried

blood spots collected on filter paper, this new methodology makes it possible to transport samples remotely for enzymatic analysis, retrospective diagnosis and population screening.[31]

GLA gene sequencing is the gold standard for diagnosing FD. Due to X-linked inheritance, there is no contribution of the mutated gene from the father to his offspring, while heterozygous females have a 50% risk of transmitting the mutated gene.[30]

Screening for Fabry disease in cerebrovascular disease

Screening for FD in high-risk populations became a major concern when enzyme replacement therapy (ERT), applied every 2 weeks, appeared in 2001. Regarding this, studies were carried out in different contexts that showed the severe complications of FD, including chronic kidney disease, left ventricular hypertrophy (LVH) and CVD. It is worth mentioning that screening may be biased towards patients with the most critical disease and classic phenotypes. In the Fabry Registry,[22] patients with CVD were diagnosed later than those without CVD, and most of them had not experienced renal or cardiac events prior to their first cerebral event, suggesting that the classic features of the disease may be absent or more subtle in these patients.

In recent times, atypical phenotypes have been reported with increasing frequency – some of which with CVD as a presenting feature –, in these cases, due to the fact that their clinical recognition requires a high index of suspicion, the diagnosis of FD is often delayed or is overlooked. Therefore, the accurate prevalence of FD in young patients with CVD is unknown.[9]

Regarding the Latin American population, there is only information from 333 patients included in the Fabry Registry,[32] mainly from Argentina, Chile, Colombia, Peru and, among them, some Mexicans. 167 Latin American women and 166 men are part of the registry, with an average age of 35.5 years for men and 37.9 years for women. Of these patients, 8 men (5%) and 3 women (2%) had CVD. Most of the Latin American patients in this registry come from nephrology and cardiology services. At the moment, there is no update of data by the Fabry Registry, whose recruitment is still open.[22]

Diagnosis and screening for FD has been a subject of study mostly in high-income countries, including neonatal screening programs. In countries such as Denmark, Australia and Japan, early detection programs — Dried blood spot testing (DBS) — have been implemented. This method uses dried blood spots on filter paper, generally obtained between 24 and 72 hours of extrauterine life, to measure enzyme α-galactosidase A activity or globotriaosylceramide accumulation.[33] These studies have managed to determine a sensitivity of 100% for the detection of newborns with FD, but with variable specificity when compared with the gold standard that is genetic sequencing (with a positive predictive value of 33 to 42%).[34] In the case of women, enzyme activity testing in blood has low sensitivity.

Treatment

In 2001, two recombinant enzymes were approved for use in Fabry disease: agalsidase alfa (Replagal®, Shire/Takeda) and agalsidase beta (Fabrazyme®, Sanofi Genzyme), called enzyme replacement therapy (ERT).[35] This therapy demonstrated a reduction in the production of LVH and in the progression of kidney disease when the clearance was less than 60ml/min/1.73m2, possibly attributed to their antiproteinuric therapy, which could lower the incidence of CVD in the long term by reducing the risk factors that promote it in both men and women. Another treatment option, Migalastat (1-deoxygalactonojirimycin; Galafold, Amicus Therapeutics) was approved in Europe in May 2016, in Canada in September 2017, in Japan in March 2018, and in the US in August of the same year, for long-term treatment of FD in adults (≥18 years of age in the United States and Canada, ≥16 years of age in other countries), with a susceptible mutation and an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m2. Orally administered, Migalastat is a small chaperone that stabilizes the endogenous α-galactosidase A enzyme and supports proper protein folding in the endoplasmic reticulum, leading to increased protein enzyme activity and stability in lysosomes of susceptible mutation carriers.[36] In a multicentric study of the use of Migalastat for 12 months (FAMOUS study), a reduction in the mass of the left ventricle was demonstrated, although it was not possible to reduce the progression of kidney disease, possibly due to the intervention of other triggering factors.[37]

In the management of FD patients with acute cerebral infarction, intravenous thrombolysis[38] or an endovascular approach can be considered; experience with the use of either in this setting is limited to non-existent, although there are no specific reasons to discard such treatments.[10]

In secondary prevention, treatment is far from satisfactory, since there is no specific therapy for cerebrovascular complications of FD. Administration of antiplatelet agents may help prevent

the atherosclerotic and thromboembolic effects of vascular endothelial damage, but experience with this approach is limited.[10] Similarly, anticoagulant agents should be considered to help prevent stroke recurrence when the implicated cause is cardiac embolism.[19]

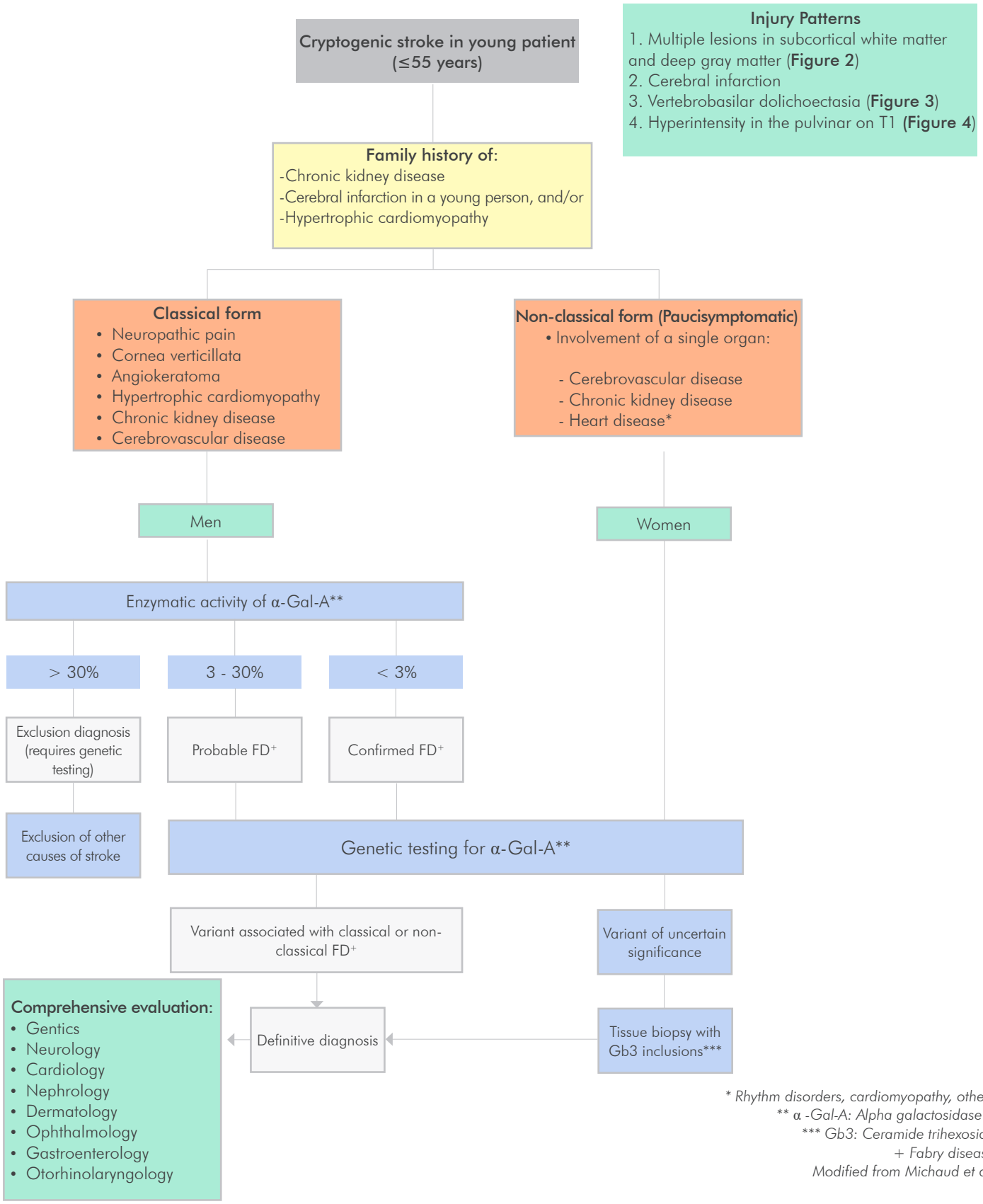
Forecast

FD is a progressive pathology with reduced life expectancy; the median survival age for men is 50-55 years, and 70 years for women. Quality of life is affected in all patients, not only due to target organ damage, but also as a result of other symptoms including gastrointestinal problems, acroparesthesias, depression, and intolerance to certain temperatures. Since its introduction in 2001, enzyme replacement therapy has been shown to be effective in relieving several of these symptoms, as well as delaying and even reversing disease progression.[7,39]

Conclusion

It is recommended that all young patients (<55 years) with a history of one or more events of ischemic or hemorrhagic CVD of undetermined etiology (cryptogenic), primarily those with systemic diseases (dermatological, cardiac or renal), undergo screening for Fabry disease, whether by determination of α-galactosidase A activity or sequencing of the GLA gene. CVD treatment in these patients is similar to that established in clinical guidelines for the general population, since there is no specific treatment for this pathology, but it requires a multidisciplinary approach[40] and follow-up (see Figure 1 on the next page).

Figure 1. Fabry Disease diagnostic algorithm



** Rhythm disorders, cardiomyopathy, others*
*** α -Gal-A: Alpha galactosidase A*
**** Gb3: Ceramide trihexoside*
+ Fabry disease
Modified from Michaud et al.

Figure 2. Axial T2-FLAIR MRI. Multiple hyperintense lesions in subcortical white matter and bilateral deep gray matter

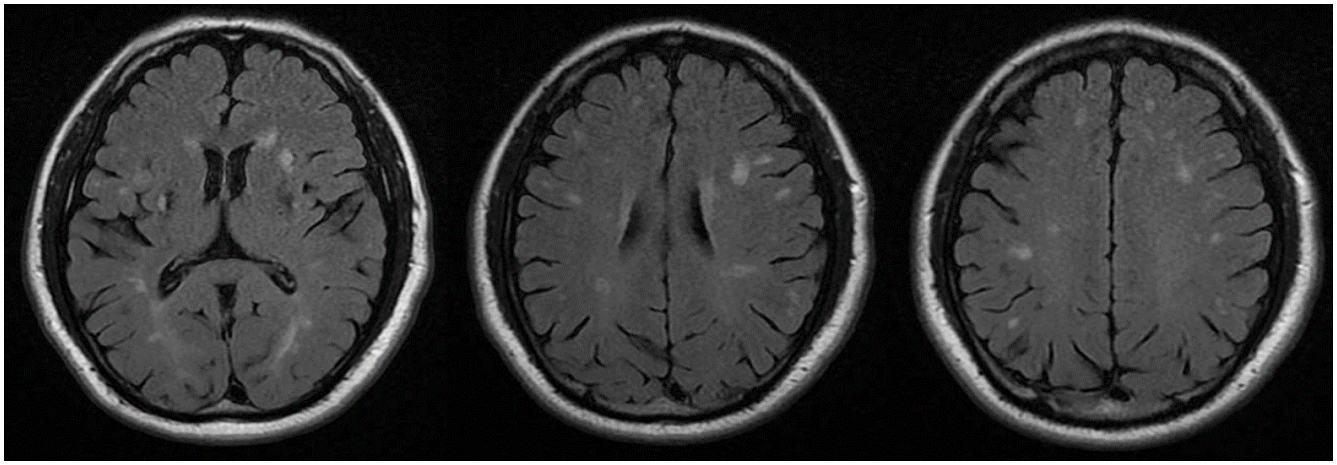


Figure 3. Coronal 3DTOF MRI. Vertebrobasilar dolichoectasia

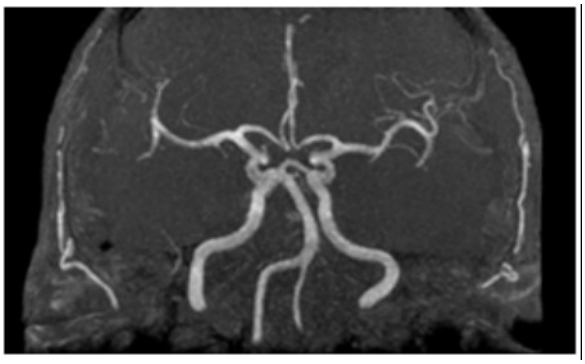
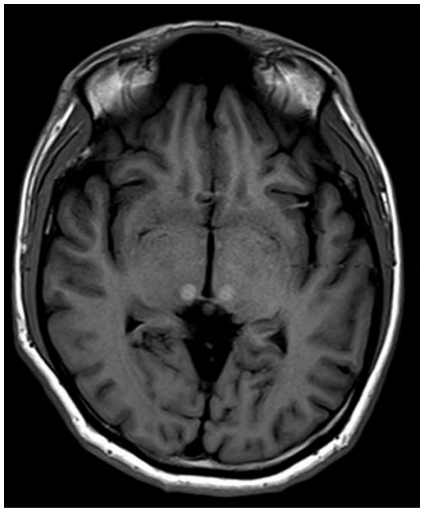


Figure 4. Axial T1 NMR. Hyperintensities in the pulvinar nuclei of the bilateral thalamus in a patient with Fabry disease. (Pathognomonic).



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Capacitación de médicos especialistas: un daño colateral de la pandemia de COVID-19

Rodríguez-Violante Mayela [1,2] | Abundes-Corona Arturo [1] | Cervantes-Arriaga Amin [1]

1. Laboratorio Clínico de Enfermedades Neurodegenerativas, Instituto Nacional de Neurología y Neurocirugía, Ciudad de México, México.
2. Clínica de Enfermedad de Parkinson y Trastornos del Movimiento, Instituto Nacional de Neurología y Neurocirugía, Ciudad de México, México.

Correspondencia

Mayela Rodríguez-Violante
Laboratorio Clínico de Enfermedades Neurodegenerativas, Instituto Nacional de Neurología y Neurocirugía.

mrodriguez@innn.edu.mx

Resumen

Introducción. La pandemia de COVID-19 ha afectado la prestación de atención médica a personas con enfermedades crónicas, como trastornos del movimiento. Los especialistas en trastornos del movimiento se vieron obligados a adaptarse a esta situación sin precedentes. El objetivo de este estudio es evaluar este impacto en términos de la reducción en el número de consultas presenciales de un programa de alta especialidad como resultado de las restricciones de la pandemia, y valorar la satisfacción general de los especialistas en entrenamiento. Métodos. Se recolectaron los registros de las consultas ambulatorias de las Clínica de Trastornos del Movimiento desde el 1 de marzo de 2020 hasta el 28 de febrero de 2021. Los datos de este período se compararon con los correspondientes a los ocho años anteriores. Se aplicó una encuesta de satisfacción junto con una escala análoga visual tanto a los pacientes como a los becarios de la especialidad. Resultados. Durante el período de estudio se realizaron un total de 1.742 consultas, lo que representa una disminución del 60% con respecto al año anterior. Además, el 38% de esas consultas se realizaron por telemedicina. La satisfacción auto-reportada de los especialistas en entrenamiento y la satisfacción del paciente con la teleconsulta fue alta (90% y 96%, respectivamente). Conclusiones. A pesar de la disminución de las visitas al consultorio, los especialistas en entrenamiento informaron una satisfacción aceptable con respecto a los objetivos de aprendizaje del programa y la satisfacción del paciente fue no comprometida.

Palabras clave: *Capacitación en trastornos del movimiento, Programa de especialidad, Pandemia, COVID-19.*

Introducción

La pandemia de COVID-19 ha afectado la prestación de atención médica a las personas con trastornos del movimiento. Además, los especialistas en trastornos del movimiento se vieron obligados a adaptarse a esta situación sin precedentes. Los hospitales académicos tuvieron que adaptarse y hacer frente a las necesidades emergentes de salud pública. El Instituto Nacional de Neurología y Neurocirugía de la Ciudad de México se sometió a una reconversión parcial para tratar a pacientes con neurocovid y pacientes neurológicos con coinfección por SARS-CoV-2.[1] Esto resultó en cambios en la programación de la clínica de pacientes ambulatorios y la reasignación de especialistas en entrenamiento y residentes, independientemente de su especialidad, a la sala de emergencias, la unidad de cuidados intensivos y las "estaciones de preselección de pacientes".

A pesar del carácter imperativo de tal adaptación, consecuencias negativas en la educación eran esperables. La mayoría de las consultas externas de la Clínica de Trastornos del Movimiento se pospusieron indefinidamente y se implementaron consultas basadas en telemedicina como una alternativa. Las teleconsultas no se habían realizado previamente en el contexto de los trastornos del movimiento en dicho centro, lo que resultó en una curva de aprendizaje pronunciada tanto para los especialistas en entrenamiento como los pacientes, quienes tuvieron que aprender a superar las dificultades tecnológicas, así como a someterse con confianza a un examen físico "virtual".

Debido a las medidas obligatorias para limitar la propagación del SARS-CoV-2, los seminarios y reuniones presenciales se cancelaron o limitaron en la mayoría de los centros médicos académicos. El objetivo de este estudio es evaluar el efecto de dichas restricciones en términos de la reducción en la cantidad de consultas presenciales de un programa de alta especialidad (Trastornos del movimiento), así como valorar la satisfacción general con el programa.

Métodos

Se recogieron los registros ambulatorios de la Clínica de Trastornos del Movimiento del periodo que va del 1 de marzo de 2020 al 28 de febrero de 2021; se consideraron tanto las consultas presenciales como las de telemedicina. Los datos de este período se compararon con los de los ocho años anteriores y se presentan como frecuencias y porcentajes.

En el caso de la consulta de telemedicina, se aplicó una encuesta de satisfacción tanto a los pacientes como a los especialistas en entrenamiento[2] de la siguiente manera: cuestionario para el paciente, posterior a la teleconsulta, ítem 17, utilizando una escala de 0 (totalmente en desacuerdo) a 100 (totalmente de acuerdo), "Estoy satisfecho con el resultado de mi consulta virtual"; y cuestionario para el médico, posterior a la teleconsulta, el ítem 14, utilizando una escala de 0 (totalmente en desacuerdo) a 100 (totalmente de acuerdo), "Estoy satisfecho con el resultado de esta consulta virtual".

Asimismo, se aplicó a los especialistas una escala analógica visual (EVA) al final de su entrenamiento —que va de 0 (muy insatisfecho) a 100 (muy satisfecho)— para evaluar su satisfacción con respecto a los objetivos de aprendizaje alcanzados. La EVA es un instrumento fiable utilizado como escala de respuesta psicométrica que mide características subjetivas o actitudes, permitiendo un número infinito de gradaciones entre puntos finales, lo que ofrece una ventaja sobre las escalas de Likert o similares, que necesitan ser exhaustivas para cubrir la totalidad del espectro de posibles respuestas.[3]

Este estudio fue aprobado por el Comité de Ética local (61/20) y se obtuvo consentimiento informado para las encuestas de satisfacción.

Resultados

Durante el período de estudio se realizaron un total de 1742 consultas. El programa de alta especialidad en Trastornos del Movimiento del Instituto comenzó en 2012. La Tabla 1 muestra el número de consultas clínicas ambulatorias en los últimos ocho años. El número de consultas mostró una tendencia ascendente hasta 2019; excepto en 2020, cuando se observa una caída del 60%. La disminución en el número de consultas brindadas por los especialistas en entrenamiento tuvo una reducción similar; sin embargo, el 38% de esas consultas se realizaron de modo virtual, lo que resultó en una reducción del 80% de consultas presenciales para la promoción 2020 en comparación con la promoción 2019. Esta tendencia también estuvo presente para procedimientos como la inyección de toxina botulínica o la programación de estimulación cerebral profunda. Los porcentajes de satisfacción de las encuestas autoinformadas, tanto del especialista como del paciente, con respecto a la teleconsulta fueron altos (90% y 96%, respectivamente). Los cuatro especialistas de la promoción del 2020 calificaron su satisfacción con respecto a los objetivos de aprendizaje con un 90 en el VAS.

Tabla 1. Número de consultas externas en la Clínica de Trastornos del Movimiento por año académico.

Año académico	Consultas ambulatorias en la Clínica	Cambio en el porcentaje	Consultas ambulatorias del programa de alta especialidad
2012	3,155	-5.54%	1,535 (48.6%)
2013	3,281	+3.99%	1,685 (51.36%)
2014	3,584	+9.23%	1,666 (46.48%)
2015	3,783	+5.55%	1,457 (38.51%)
2016	3,838	+1.45%	1,496 (38.94%)
2017	3,868	+0.78%	1,543 (39.89%)
2018	4,124	+6.62%	1,609 (39.01%)
2019	4,414	+7.03%	1,874 (42.5%)
2020	1,742	-60.53%	633* (36.3%)

* Incluye 240 teleconsultas

Discusión y conclusión

Antes de la pandemia de COVID-19, las herramientas digitales para la educación no formaban parte de los programas de formación médica; sin embargo, tuvieron que implementarse con urgencia para limitar los efectos negativos de las restricciones pandémicas. Las encuestas aplicadas en este estudio han intentado evaluar la efectividad de la educación a distancia en este contexto. En general, se mantuvo un buen nivel con respecto a la adquisición de conocimientos y la satisfacción percibida de los especialistas en entrenamiento a pesar del cambio sustancial en la modalidad educativa.[4] Recientemente se ha investigado sobre la viabilidad de la capacitación remota para el programa de especialización en trastornos del movimiento. Las dificultades más evidentes implican aspectos clínicos que no se pueden evaluar remotamente, como el tono, los reflejos y pruebas de sensibilidad.[5] Las ventajas incluyen un mayor acceso para los pacientes y una disminución de los problemas de programación. En este estudio, la satisfacción de los especialistas en entrenamiento fue en general positiva (69%), aunque no óptima.[5]

En nuestro centro, a pesar de la drástica disminución de las visitas a consultorio, los especialistas reportaron una satisfacción aceptable con respecto a los objetivos de aprendizaje del programa. Además, los porcentajes de satisfacción autoinformada de médicos y pacientes en relación a la teleconsulta fueron altos (90% y 96%, respectivamente). La pandemia ha implicado adaptaciones que han promovido mejorías en la telesalud, un campo en rápida evolución.[6]

La disponibilidad de la vacuna COVID-19 probablemente generará una normalización parcial de las visitas al consultorio, sin embargo, no deben olvidarse las lecciones en relación a la capacitación remota de especialistas y la ampliación de sus competencias.

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Case Report | ARCHIVOS DE NEUROCIENCIAS

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Tolosa-Hunt syndrome associated with Coronavac / Sinovac vaccination against Covid-19

Molina-Martínez Rodolfo Pedro [1]✉ | Vega-Moreno Daniel Alejandro [1] | Ochoa-Mena José Darío [2]

López-Zapata María del Rosario [2] | García-González Ulises [1,2]

1. Department of Neurosurgery. South Central Hospital of High Specialty, Mexican Petroleum, Mexico City.

2. Department of Neurology. South Central Hospital of High Specialty, Mexican Petroleum, Mexico City

Abstract

Tolosa-Hunt syndrome consists of unilateral or periorbital headache, paresis of the III, IV, and/or VI cranial nerves ipsilateral to the headache; along with image evidence of pathology in the cavernous sinus or superior orbital fissure. We present the case of a 76 YO woman who developed Tolosa-Hunt syndrome posterior to the application of Sinovac vaccine against Covid-19.

Keywords: *Covid-19, Tolosa-Hunt, Sinovac, Coronavac.*

Correspondence

Dr. Rodolfo Pedro Molina Martínez. Anillo Periferico, Num. 4091, Col. Fuentes del Pedregal, Alcaldía Tlalpan, C.P. 14140, Ciudad de México, México.

✉ rpmolinam@gmail.com

Introduction

Tolosa-Hunt syndrome (THS) – originally described by Tolosa and later by Hunt in the mid-20th century consists of unilateral painful ophthalmoplegia, with involvement of the cranial nerves responsible for eye movement and ipsilateral facial sensory loss. This syndrome can occur due to multiple causes at the cavernous sinus or the superior orbital fissure. However, it has been acknowledged as a unilateral inflammatory process of unknown etiology.[1] This case report intends to address a new etiology for Tolosa-Hunt syndrome as well to inform of a new possible side effect of the Covid-19 vaccination.

Clinical case

We present the case of a 76 YO woman, resident of Mexico City, with the following personal history: quinolones allergy, systemic arterial hypertension, non-insulin-dependent diabetes mellitus, and irritable bowel syndrome. The patient completed Coronavac / Sinovac vaccination scheme (1st dose March 21, 2021, 2nd dose May 5, 2021) and came to the emergency department due to oppressive headache of mild intensity and pain at the puncture site on the day of application of the first dose. The patient presented to the emergency room four more times after the application of the second dose; all of them were diagnosed as hypertensive emergencies and the patient was discharged with adjustment of her antihypertensive medications. On June 07, 2021, she went to the emergency department for the 5th time due to oppressive headache 9/10 visual analogue scale (VAS), phonophobia, and right ear pain, she was then assessed by the neurology service, and a computed tomography scan of the skull was performed, which reported as normal, ruling out structural causes. On June 09, 2021, she came again presenting photophobia, right ptosis, and right eye pain which exacerbated with movement; laboratory exams showed severe hyponatremia (116 mmol / l) and for this reason she was admitted at the internal medicine department for treatment and diagnostic protocol.

During her hospitalization, she was evaluated again by the neurology service. On physical examination, she presented pain facies, hyporexia, right oppressive-stabbing hemicranial headache, 7/10 VAS, photophobia – which conditioned her to wear an eye mask –, incomplete palsy of the right third cranial nerve without pupillary involvement, palsy of the right IV cranial nerve, as well as diplopia – which improved with the Bielschowsky maneuver –, pain on right eye movement and hypoesthesia in right V1 and V2. Palsy of right VI nerve was also noted (Figure 1).

Laboratory studies and a lumbar puncture were performed, which only showed a unique alteration in previously known sodium levels (Table 1). Magnetic resonance imaging (MRI) was requested, which exhibited right cavernous sinus enhancement (Figure 2). With the clinical data obtained through physical examination and imaging studies, as well as the absence of alterations in laboratory studies, the diagnosis of Tolosa-Hunt syndrome was established. Management started with high doses of corticosteroids (dexamethasone 8 milligrams intravenously every 8 hours), with improvement of the previously described symptoms, and she was discharged with prednisone at a dose reduction scheme.The patient had a last consultation on June 28, 2021, in which an improvement in her symptoms was observed, and no extraocular movements deficit were registered (Figure 3).

Figure 1. Extraocular eye movements pre-treatment

Table 1. Laboratory tests

Laboratory test	Result
Leucocytes	8.82 103/ul
Hemoglobin	15.30 gr/dl
Hematocrit	41.80 %
Platelets	363 103/ul
Glucose	116 mg/dl
Glycosylated hemoglobin	6.5 %
Urea	19.9 mg/dl
Creatinine	0.64 mg/dl
Aspartate aminotransferase	26 u/l
Alanine aminotransferase	14 u/l
Lactate dehydrogenase	164 u/l
Total bilirubin	0.53 mg/dl
Sodium	121 mol/l
Potassium	4.6 mmol/l
Chloride	86 mmol/l
Prothrombin time	17.2 seconds (70% activation)
Partial thromboplastin time	36.9 seconds
INR	1.28
Lumbar puncture	
Aspect	Clear
Total cells	2 cells/ul
Leucocytes	2 cells/ul
Total protein	21.2 mg/dl
Glucose	99.5 mg/dl
Gram stain	negative
Ziehl-Neelsen stain	negative

Figure 2. Magnetic resonance image. Axial view, T1 weighted. Enhancement of the right cavernous sinus is noted (red arrow)

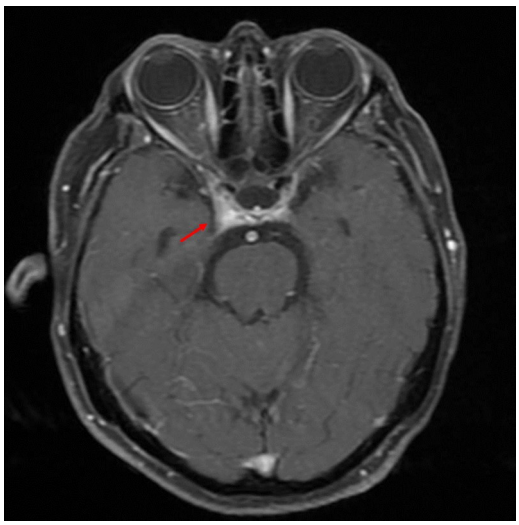
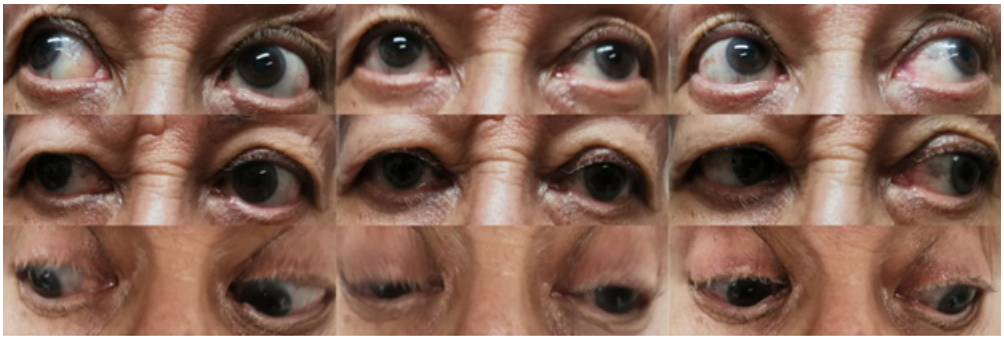


Figure 3. Extraocular eye movements post-treatment



Discussion

The International Headache Society presents in the third edition of its classification (ICHD-III) the criteria for the diagnosis of Tolosa-Hunt syndrome. These correspond to unilateral or periorbital headache with evidence by MRI or biopsy of granulomatous inflammation of the cavernous sinus, superior orbital fissure or orbit, as well as paresis of the III, IV, and/or VI cranial nerve ipsilateral to the headache, not attributable to another diagnosis of ICHD-III.[2]

The diagnosis of Tolosa-Hunt syndrome is one of exclusion. Regarding this case, chronic hyponatremia was diagnosed as a result of long time medication with diuretic. Tolosa-Hunt syndrome has also been associated with poorly controlled diabetes mellitus; a previous clinical case has been reported, however, the registered glucose level was higher compared to that of our patient[3] (glycosylated hemoglobin of 12.4% *vs*. 5.6%). Another case of painful ophthalmoplegia and ipsilateral ptosis was reported in Papua New Guinea regarding a non-previously diagnosed diabetic patient; clinical diagnosis of supraorbital syndrome was made, nevertheless, the patient did not respond to prednisolone, thus not supporting the diagnosis of Tolosa-Hunt syndrome.[4] Sarcoidosis if one of the leading causes of Tolosa-Hunt syndrome, however our patient did not have a previous medical history that suggested she had experienced such disease prior to vaccination: her medical examination did not concurred with clinical findings of sarcoidosis.

The inactivated SARS-CoV-2 vaccine by Sinovac has been previously reported to cause neurological disorders such as acute disseminated encephalomyelitis, headache, and myalgia.[5] A case of complete paralysis of the oculomotor nerve was reported in January 2021, two weeks after the application of the vaccine against influenza – which is similar to Sinovac as both are inactivated in Vero cells. This vaccine is known to cause Guillain-Barre syndrome, demyelinating polyneuropathy, and disseminated encephalomyelitis, among others.[6]

A case of Tolosa-Hunt syndrome was reported most recently, however, this was with mRNA-based Covid-19 vaccine.[7] This continues the discussion on the side effects of vaccines against Covid-19, whether exacerbating previously acquired unknown conditions, or being the cause of such.

We strongly believe that the benefits of vaccination outweigh its possible side effects. However, proper documentation of side effects – whether from the vaccine itself or from conditions attributed to the patient – must be conducted and investigated.

Conclusion

The diagnosis of Tolosa-Hunt syndrome is one of exclusion.The absence of risk factors, as well as the lack of clinical, laboratory, and/or image supporting the diagnosis of another type of pathology, along with the onset of symptoms after its application, leads to consider vaccination against Covid-19 as a possible cause of Tolosa-Hunt syndrome, which must be included in the differential diagnosis of such disease.

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