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Research Article

A Novel Sign for Cerebellar Lesions Detection Based on Cognitive Functions

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Abstract

The cerebellum has been related almost exclusively to motor functions, in spite of the growing evidence that relates the cerebellum to cognitive functions. We describe a clinical maneuver and sign designed to detect cerebellar lesions, based on cognitive function evaluation.

Objective: To determine the usefulness of the proposed maneuver to detect or exclude cerebellar lesions as a diagnostic test.

Materials and Methods: 69 volunteers distributed in 3 groups participated: Group 1 (n=15): Patients with exclusively cerebellar lesions demonstrated by MRI; group 2 (n=30): healthy subjects with normal cranial MRI; group 3 (n=24): healthy subjects without imaging studies. We evaluated 4 neuropsychological test results in all groups, in sitting position and Romberg´s position.

Results: If there is fluent agrammatic narration or the patient cannot narrate in Romberg´s position, the clinical sign is positive and the possibility of having a paleo or neocerebellar lesion increases 28.6-fold. **Conclusions:** These results demonstrate that there is evidence of paleo and neocerebellar participation in narration. The clinical maneuver and sign described can be useful to detect paleo or neocerebellar lesions.

Background

The traditional functional concept of the cerebellum is that it is essential for motor, posture and proprioceptive coordination, together with the posterior white columns, visual pathway and vestibular system; that it is responsible for balance and that it plays an important role in speech and sight control [1-4]. Due to the dramatic motor deficits caused by cerebellar lesions, and as intellectual functions seem to be preserved, the increasing evidence that establishes that the cerebellum participates in cognitive functions has not been entirely accepted until recently.

In the last few decades we have seen important advances in physiology and diagnostic technology, but not as many in bedside clinical localization. We describe a clinical maneuver and a sign that explore the cognitive functions of patients with cerebellar lesions, comparing them to controls for cerebellar lesion detection.

Cerebellum and Cognition

According to the functional atlas of the cerebellum [5], the front and the rear crux (right ansiform lobule) and vermis VIIA-f (folia) are activated during the execution of language, and attention activates the left front crux. Based on this assertion, there is a possible correlation between specific cerebellar lesions in these areas and the phenomenon that we have defined as "*fluent agrammatism*" and other cognitive dysfunctions described in the following sections.

The cerebellum has been studied since the IV century BC and our concept of it has changed through time. [6-16]. Adults with cerebellar degeneration can present with psychotic symptoms [17]. In patients with psychotic symptoms and cognitive deficits, degeneration or cerebellar tumors were found in autopsies [18]. Cognitive deficiencies are well known in patients with Friedreich´s ataxia [19] and olivopontocerebellar atrophy. Botez stated the influence of the cerebellum in cognitive functions in patients intoxicated with phenytoin [20]. Autism has been frequently related with cerebellar abnormalities [21-24].

A new perspective on cerebellar functions includes prediction and preparation for processing, analysis or action, and answering [23, 24]. It plays an important role in learning, anticipation [25] and planning operations [26-29]. Right ischemic cerebellar lesions can cause agrammatism limited to spontaneous language [30-32]. The cognitive-affective cerebellar syndrome is characterized by alterations in executive functions, space and visuospatial orientation, personality changes and language difficulties that include dysprosody, agrammatism and moderate anomia. [33].

Agrammatism is a dysfunction of the production and comprehension of grammatical structures that include functional words such as articles, prepositions or auxiliary verbs and word terminations, with meaning preserved - in most cases - due to the presence of nouns [34].

Romberg's Test Physiology

Thalamocortical connections, corticofugal projections to reticulospinal and vestibulospinal tracts, direct corticospinal projections to the spinal cord, and projections to the basal ganglia and cerebellum all have an active role in the planning and execution of movements. The cerebellum and basal ganglia are critically important for motor function. The cerebellum has a major role in the coordination of movement, the control of equilibrium and muscle tone. The cerebellum controls the ipsilateral limbs through connections with the spinal cord, brainstem and contralateral motor cortex through the thalamus [35]. Romberg's maneuver tests the functional integrity of the proprioceptive impulses through the posterior white columns, medial lemniscus and cerebellum to maintain balance during visual deprivation [3].

Methodology

Materials and Methods

Objective: To determine the usefulness of the proposed maneuver to detect or exclude cerebellar lesions as a diagnostic test. Study design: diagnostic test. Study universe (n= 69). Group 1 (n=15): Patients with exclusively cerebellar lesions demonstrated by MRI. Etiology: Hemangioblastoma= 5 (33.3%), meningioma= 3 (20%), Chiari malformation type I= 2 (13.3%), Arteriovenous malformation= 1 (6.7%), cavernous hemangioma= 1 (6.7%), dermoid cyst= 1 (6.7%), medulloblastoma= 1 (6.7%), single metastatic tumor= 1 (6.7%). Lesion topography: Right hemisphere= 8 (53.3%), left hemisphere= 1 (6.7 %), pancerebellar= 1 (6.7 %), vermis= 3 (20%), cerebellar tonsils = 2 (13.3%). Group 2 (n=30): Healthy subjects without clinical history or data that suggested a neurologic or metabolic disease, with normal neurological examination and normal cranial MRI. We included patients with unilateral neurovascular decompression for hemifacial spasm and with trigeminal neuralgia. Group 3 (n=24): Healthy subjects without clinical evidence suggesting a neurologic or metabolic disease, without imaging studies. Inclusion criteria: Case group: Patients with exclusively cerebellar lesions, demonstrated by clinical history, exploration and MRI, able to maintain Romberg's position during the test, who volunteered to participate in the study. Control group with MRI: Healthy volunteers with diagnosis of trigeminal neuralgia or hemifacial spasm, asymptomatic during the test, with normal MRI, who agreed to participate in the study, with no previous knowledge of this test. Control group without MRI: Healthy volunteers, without clinical evidence suggesting a neurologic or metabolic disease, without MRI, paired with the case group, and with no previous knowledge of this test. The ethics committee of the National Institute for Neurology and Neurosurgery in Mexico approved this study.

Maneuver For Cognitive Function Exploration With Cerebellar Activation

The maneuver consists of the application of 4 neuropsychological standardized tests to all participants, in two different stages. During the first stage, the tests were applied in the sitting position. During the second stage, equivalent standardized activities were applied in Romberg's position. We included 4 different tests. Narration and the 3 remaining tests (mental control, category evocation and word memorization) were included as control tests to rule out the possibility that an abnormal result in narration could be the consequence of being focused on the maintenance of balance.

First Stage: Sitting Position.

Verbal fluency with a phonological cue: They were asked to list the highest number of words beginning with the letter "p", during 30 seconds. **Mental control**: 3 by 3 successive subtractions, beginning with the number 25, in a 30 second limited period of time. **Word memorization**: An oral list of 5 unrelated words was given. The subject had to memorize and repeat them in the correct order within a maximum of 3 attempts. **Narrative language**: They were asked to narrate a defined topic ("market") during a 30 second time period.

Second Stage: Romberg's Position.

The subjects of the 3 groups were asked to keep Romberg´s position for around 15 seconds to allow them to stabilize and later on, they were asked to keep this position with their eyes closed and perform the following tests: **Verbal fluency with a phonological cue**: the letter "T". **Mental control**: Successive subtractions 3 by 3, beginning with the number 24. **Word memorization**: Another set of 5 unrelated words was used. **Narrative language**: "School" was chosen as the topic.

The Maneuver And Interpretation Of Sign Results

All results were audio or film recorded for further analysis and scored by each adviser. The final score was a consensus. The results were scored according to the following criteria for each activity.

Operational Definition And Variable Measurement

Verbal fluency with phonological cue: The final score was the total number of words produced in the assigned period of time. Normal: 6 words in 30 seconds.

Word memorization: The participant was asked to memorize the correct order in a maximum of 3 attempts. One point was assigned to each correct word listed in the correct order. They were marked "Possible" or "Impossible".

Mental control: "Correct" (including mistakes with spontaneous corrections made during the assigned period of time) or "Impossible".

Narrative language: Fluency was analyzed (fluent or not fluent), content (related or not related) and grammatical structure (correct: 2 points, if agrammatical: 1 if there was a pivot word that would facilitate the listing of words, and 0 for just listing a string of nouns.

Statistical Analysis

A univariate analysis was carried out to set up the group´s distribution curves. U Mann-Whitney and Fisher tests were carried out, and a logistic regression test for the significant variables. Sensitivity, specificity, precision, predictive positive and negative values, kappa agreement test, positive and negative probability, error and diagnosis odds ratio (OR), Youden´s J test, positive and negative predictive precision were calculated to determine the usefulness of the proposed maneuver to detect patients with cerebellar lesions and to identify the absence of these lesions in healthy subjects as a diagnostic test. Correlation tests were carried out as required.

Security and Ethical Aspects

Due to the non-invasive nature of the test, the volunteers were not exposed to any risk and human investigative ethics were respected.

Results

We included 69 subjects distributed in 3 study groups. The general data of all groups are described in table 1. There were significant differences in age, gender and years of scholarship.

GENERAL DATA	CONTROL WITH MRI n = 30	CONTROL WITHOUT MRI N = 24	CASES n = 15
AGE (years)			
Average +/- DE	55.8 ± 11.0	34.8 ± 9.7	33.6 ± 12.1
Median (Range)	54.0 (34-73)	35.5 (19-58)	31.0 (19-52)
GENDER (%)			
Male	5 (16.7)	11 (45.8)	7 (46.7)
Female	25 (83.3)	13 (54.2)	8 (53.3)

HAND LATERALITY (%)			
Right-handed	29 (96.7)	23 (95.8)	15 (100.0)
Left-handed	0 (0.0)	1 (4.2)	0 (0.0)
Ambidextrous	1 (3.3)	0 (0.0)	0 (0.0)
EDUCATION			
Median (Range)	6 (2-17)	12 (6-16)	6 (2-16)

Table 1.

General data. Only 3 tests showed significant differences: narration in sitting position comparing the case group with the control group 2 (p=0.05), category evocation in Romberg's position comparing both control groups (p = 0.02) and narration in Romberg's position comparing the case group with both control groups (p= < 0.001).When analyzing the results of the association between the results of the neuropsychological tests in all groups, the results of the narration test were statistically significant for both experimental situations with an OR (CI $_{95\%}$) of 13.2 (1.2-138.6) for narration in the sitting position and of 28.6 (5.5-147.3) for narration in Romberg´s position (table 2).

NEUROPSYCHOLOGICAL TESTS	OR (CI 95%) Cases vs. Controls (group 1+2)	P Value
Mental control in Sitting Position	0.66 (0.2-2.1)	0.49
Category Evocation in Sitting Position	1.03 (0.2-3.7)	0.95
Word Memorization in Sitting Position	0.57 (0.06-5.1)	0.61
Narration in Sitting Position	13.2 (1.2-138.6)	0.03
Mental control in Romberg	0.7 (0.2-2.2)	0.57
Category Evocation in Romberg	0.9 (0.7-1.0)	0.22
Word Memorization in Romberg	1.3 (0.3-4.4)	0.67
Narration in Romberg	28.6 (5.5-147.3)	< 0.001

Table 2.

Assessment of the association between neuropsychological tests in patients with cerebellar lesions against control subjects without cerebellar lesions (OR raw data).

We included the significant variable results in the previous analysis in a logistic regression equation. The variables that remained constant were age (p = 0.04), scholarship (p=0.03) and narration in Romberg's position (p= < 0.001). The variables that lost their statistically significant value were: gender and category evocation. Finally we evaluated the usefulness of the clinical maneuver and sign as a diagnosis test in both experimental conditions. It failed to predict the presence of a cerebellar lesion in sitting position. Even so, the narration test in sitting position shows a high specificity with an OR of 13.25, but low sensitivity.

In table 3, the results of a diagnostic test in Romberg's position are shown, the narration test proving useful to predict the presence of a cerebellar lesion, with a sensitivity of 0.86 and specificity of 0.81. The OR diagnosis is of 28.6 (p = < 0.001) and Youden´s J = 0.68.

Discussion

Study Groups

Significant differences due to age and education were evident. The age of the case group and of group 3 is significantly lower than the age of group 2, and the total years of education were higher in group 3. Even if this could be considered a limitation for a cognitive evaluation study, we consider that these differences do not constitute a disadvantage for our case group as it did not influence the final statistical analysis.

Cerebellum and Cognition

Scientific evidence of the role of the cerebellum in complex cognitive processes like language, learning and attention is growing (5-33). From a theoretical point of view, the dento-rubro-thalamo-cortical circuit is the anatomical basis that supports the motor and cognitive functions of the cerebellum, but the precise cerebellar mechanisms (the way in which they are planned, executed and corrected almost simultaneously during motor and cognitive activities) are still not completely clear. Exploring the cognitive functions of the cerebellum presents technical difficulties that have limited its research. Several functional MRI studies have established evidence of the cerebellar role in cognition processes (36, 37), but these images are acquired with the patient resting and in supine position, when there is almost no cerebellar motor function.

Tests	Kappa	Sensi-tivity	Speci-ficity	VP (+)	VP (-)	OR Diagnosis	OR Error	Youden´s J	PV (+)	PV (-)
Narration	0.571	0.866	0.814	4.68	0.164	28.6	1.477	0.681	0.565	0.957
Mental Control	0.053	0.6	0.4815	1.157	0.831	1.393	1.615	0.081	0.243	0.813
Category Evocation	0.254	0.666	0.666	2	0.5	4	1	0.333	0.357	0.878
Word Memorization	0.05	0.333	0.722	1.2	0.923	1.3	0.192	0.056	0.25	0.796

Table 3.

Results as a diagnostic test in Romberg's position: VP (+) = Positive probability; VP (-) = Negative probability; OR Diagnosis= "Odds Ratio" Diagnosis; OR Error= "Odds Ratio" of Error; PV (+) =Positive Predictive Value; PV (-) = Negative Predictive Value.

The cerebellum is essential for the execution of specific activities, a series of different events in a particular context and specific status at specific moments. Any clinical maneuver designed to explore the cognitive functions of the cerebellum has to include these particular characteristics. We consider that exploring the patients in 2 experimental situations, using the clinical maneuver previously described, offers an experimental advantage, making it possible to activate the physiological context in which the cerebellum participates.

The Sign

When a patient with paleo or neocerebellar pathology is isolated from visual afferents and keeps a non-habitual position, like Romberg´s, a vast amount of information must be processed to maintain balance, in which the cerebellum participates. We postulate that if a person has to perform cognitive activities while maintaining Romberg's position, the cerebellum is overloaded with functional stress and it focuses its functions in a hierarchical manner on the maintenance of balance, and does not execute other simultaneous functions as well, such as cognitive.

We designed this clinical maneuver in which 4 different neuropsychological tests are used to evaluate the participants in 2 different experimental situations. In the sitting position, patients and controls can execute the cognitive tests exclusively with archicerebellar motor participation. When applying equivalent cognitive activities in Romberg's position, the physiological situation changes dramatically. In this situation, the cerebellum must simultaneously participate in both cognitive and more complex motor activities, showing a lower performance on the cognitive test execution in patients with paleo or neocerebellar pathology.

Even if the variables that were statistically significant were 3 - narration in sitting position comparing the case group without MRI ($p= 0.05$); category evocation in Romberg's position comparing both control groups ($p= 0.02$) and narration in Romberg's position comparing the case groups with both control groups ($p= < 0.001$) - only narration in Romberg's position withstood logistic regression analysis ($p= < 0.001$).

We postulate that paleo or neocerebellar lesions can interfere with the execution of cognitive tasks such as narration when under functional stress, but when the execution of cerebellar motor functions is added simultaneously, as in the case of Romberg´s position, they do not affect other neuropsychological test results such as mental control, category evocation and memory. The Chiari type I patients with archicerebellar pathology, did not show these phenomena. The control groups did not show a significant deterioration in the execution of the same tests under the same experimental conditions. It is of special interest to investigate the reason why the activity most affected while in Romberg's position is narration, and not the other cognitive processes evaluated. A different methodology is required.

Many neurological syndromes and signs are detected based on narration dysfunctions with localization value such as Broca´s and Wernicke´s aphasias, Gertsmann-Straussler-Scheinker syndrome, among others, but fluent agrammatism has not been previously described. We defined as fluent agrammatism the emission of a correct number of words per minute, but as a list of nouns, with no grammatical construction (teacher, classroom, chair, chalkboard, book). We observed fluent agrammatism in most of the patients during narration in Romberg´s position.

If the patient can narrate in the sitting position, but cannot narrate or shows fluent agrammatism, then the sign is positive and the risk of having a cerebellar lesion increases 28.6-fold.

Conclusions

The first maneuver and sign for clinical exploration and cerebellar lesion detection, based on the evaluation of cognitive functions is described, and opens up a new perspective for research in the field of neurology and in neuropsychology. If the sign described is positive, the risk of having a cerebellar lesion increases 28.6-fold. It is of special interest to study "fluent agrammatism", a phenomenon that has not been previously described. The fact that the application of the maneuver has no cost and that it can be carried out within a short period of time is a great asset. More research is needed using both clinical and paraclinical methods to understand better brain and cerebellar interaction.

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Dr. Enrique de Font-Réaulx Rojas is the principal and corresponding author and designed the clinical maneuver and sign interpretation. He wrote the protocol and recruited the participants, and participated in all the stages of the protocol.

Ana Ruth Díaz-Victoria and María del Rosario Ramos Cuevas are the neuropsychologist who helped to design the maneuver and participated in the evaluation of the tests.

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