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Anomalies in the cognitive-executive functions in patients with Chiari Malformation Type I

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Abstract

Background: Over the last decade there has been growing evidence that neuropsychological deficits, principally in the executive functions, may be involved in the pathogenesis of Chiari Type I disease. The aim of this study is to compare changes in cognitive function in patients with Chiari Type I and healthy subjects. **Method:** The neuropsychological profile of these patients was compared with healthy controls. Three neuropsychological tests were administered to both Chiari Type I patients and healthy controls to assess the frontal executive functions of vigilance or selective attention, mental flexibility, planning and concept formation. **Results:** The results suggest that Chiari Type I patients are affected in the processes of inhibition and self-control as well as in attention capacity and maintaining a course of thought and action. **Conclusions:** These results provide evidence of possible deficits or anomalies in the cognitive executive functions of patients with Chiari Type I.

Keywords: Chiari Type I, frontal executive functions, neuropsychological assessment, Stroop.

Resumen

Anomalías en las funciones cognitivo-ejecutivas en pacientes con la Malformación de Chiari Tipo I. **Antecedentes:** en la última década, existen evidencias crecientes de que déficits neuropsicológicos, esencialmente en funciones ejecutivas, pueden estar involucrados en la patogenia de la enfermedad de Chiari Tipo I. El objetivo del estudio es evaluar la influencia de anormalidades estructurales sobre las funciones neuropsicológicas, fundamentalmente ejecutivas, en pacientes con Chiari Tipo I. **Método:** para ello se comparó el perfil neuropsicológico de estos pacientes con controles sanos. Tanto a los pacientes Chiari Tipo I como a los controles sanos se les aplicó pruebas neuropsicológicas que valoraron funciones ejecutivas frontales de vigilancia o atención sostenida, flexibilidad mental, y planificación y formación de conceptos (Stroop, CPT, WCST). **Resultados:** los resultados obtenidos sugieren una afectación de los pacientes Chiari Tipo I en los procesos de inhibición y autocontrol (Stroop) y en la capacidad atencional y en el mantenimiento del curso del pensamiento y la acción (WCST). **Conclusiones:** estos resultados proporcionan evidencias de posibles déficits o anomalías en las funciones ejecutivas cognitivas, que permitirían diferenciar los pacientes con Chiari Tipo I.

Palabras clave: Chiari Tipo I, funciones ejecutivas frontales, evaluación neuropsicológica, Stroop.

Traditionally, the cerebellum has been directly related to postural control, walking gait and fine voluntary movements (Javalkar, Khan, & Davis 2014; Marvel & Desmond, 2010), however, since the early nineteenth century, there have been numerous cases of patients presenting atrophy and cerebellar degeneration who also have non-motor deficits, especially those related to cognitive processes (Buckner, 2013; Schmahmann, 2004; Schmahmann & Sherman, 1998). Adams, Schatzki, & Scoville (1941) recognized five syndromes into which these deficits could be grouped: Intracranial hypertension syndrome, cranial nerve impairment, bulbar compression syndrome, medullary syndrome and cerebellar syndrome.

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Phylogenetically the cerebellum has contributed to increasingly complex cognitive processes including the executive functions, learning, procedural and declarative memory, language processing, and the visual-spatial and affective functions (Allen et al., 2014; Chen, Ho, & Desmond, 2014a; D'Angelo & Casali, 2013; Tirapu, Luna, Iglesias, & Hernáez, 2011). In the last two decades of the 20th century, ample evidence was produced regarding the non-motor functions of the cerebellum (Bolduc et al., 2011; Koziol et al., 2014; Noroozian, 2014; Tedesco et al., 2011). In general, the list of cognitive functions that may be affected by cerebellar damage are numerous and varied, and they include the following: Working memory (Boehringer, Macher, Dukart, Villringer, & Pleger, 2013; Lacy, Ellefson, DeDios-Stern, & Frim, 2016), verbal memory (Marvel & Desmond, 2010), learning (Shin & Ivry, 2003), executive functions (Bellebaum & Daum, 2007; Gottwald, Wilde, Mihajlovic, & Mehdom, 2004) and language (De Smet, Paquier, Verhoeven, & Mariën, 2013). Schmahmann & Sherman (1998) proposed the term "cerebellar cognitive affective syndrome" to encompass alterations in the executive functions, in visual-spatial skills, in language or personality changes. Recent experimental evidence emphasizes the key role that the cerebellum plays in cognition and the emotions (Klein, Hopewell, & Oien, 2014; Schmahmann & Caplan, 2006).

Among the possible malformations of the craniocervical junction, Chiari malformation Type I is notable for its frequency and it is defined as a set of congenital anomalies of the metencephalon that result in abnormal relations between various structures: The cerebellum, the cerebellar tonsils, the medulla oblongata, the cervical medulla and the base of the skull. Classically Chiari Malformation Type I (CM-I) (Chiari, 1987) has been described as the abnormal descent of the cerebellar tonsils, at least 5 mm below the *foramen magnum*. Secondarily it may be associated with the formation of a cavity in the spinal cord, a condition known as *syringomyelia*, in 32% to 88% of cases (Guinto et al., 2004; Oldfteld, Muraszko, Shawker, & Patronas, 1994). This type of syndrome may be presented clinically with a wide variety of signs and symptoms of insidious and progressive origin, suggesting a lesion in the cerebellum, the brainstem, the upper portion of the cervical spinal cord or the cranial nerves. The most common symptom in adults is the suboccipital headache (McVige & Leonardo, 2015), in up to 60-70% of cases, but dizziness, ataxia, and neuropathy of the last cranial nerves can also manifest, as well as dysphagia and dysphonia, spastic tetraparesis and sensory loss (Grazzi & Andrasik, 2012). The lack of consensus on the pathogenesis of CM-I is a well-established fact (Loukas et al., 2011), although in recent years an abnormally small size of the posterior fossa has been confirmed, probably secondary to an alteration in the mesoderm. This would make the lack of space and the increased pressure cause the descent of the cerebellar tonsils.

Currently the role of the cerebellum in the modulation of the higher cognitive functions is becoming increasingly clear (Chen et al., 2014a; Van Overwalle, Baetens, Mariën, & Vandekerckhove, 2014). Patients with Chiari I have behavioral disorders with impairments in the executive functions, verbal fluency, abstract thinking and working memory (Koziol & Barker, 2013). Leiner, Leiner, & Dow (1986) suggest that the involvement of the cerebellum in the cognitive functions, especially in its lateral structures, responds to the connections it maintains with the prefrontal cortex (Chen et al., 2014b). These connections with the prefrontal lobe enable it to “improve” the mental skills; the connections with the Broca area allow it to “improve” the language skills and the connections to the motor cortex permit it to “improve” the fine motor skills (Ardila, Bernal & Rosselli, 2016; Leiner, Leiner, & Dow, 1989). Clinical research shows how patients with Chiari I have subjective complaints in a wide range of neuropsychological functions (attention, executive functions, working memory) that could be involved in the pathogenesis and could respond to mechanisms of crossed cerebellar diaschisis (Baillieux, et al., 2010; Starowicz-Filip, Milczarek, Kwiatkowski, & Bętkowska-Korpała, 2013). Within this context, the objective of this research is to study the influence of structural abnormalities on the cognitive functions in patients with Chiari Type I. The neuropsychological profile of these patients is compared with healthy controls in order to provide data on the relationship between the cerebellum and the neocortex with regards to the executive functions, and in order to determine whether these changes are a key pathophysiological component of this malformation. The aim is to understand whether these alterations have a characteristic pattern in Chiari Type I disease. In order to achieve this objective not only will patients with Chiari Type I be evaluated but also healthy controls.

Method

Participants

A total of 20 people, 6 men (33.3%) and 14 women (66.6%), between the ages of 38 and 60 (mean = 47.95; SD = 6.70) were included in the study. All of them met the criteria for being classified, using cranio-spinal MRI, as having Type I Chiari syndrome without hydrocephalus and a descent of more than 5 mm into the foramen magnum. All non-operated patients with Chiari I were consecutively elected, attended by the Neurosurgical Service of the Hospital Centro Médico of Asturias (Spain). The control group included 20 participants, of whom 10 were men (55%) and 10 were women, aged between 18 and 53 (mean = 32.38, SD = 12.51), who did not have any physical or psychological pathology (neurological disease, major psychopathology, multiple organ pathology, neoplasm, dependence on psychotropic drugs or other drugs) that required medical intervention or medication. No significant differences were observed in age, civil status, and educational level among the people from the experimental and control groups.

The study was approved by the Ethics Committee of the Hospital Centro Médico, respecting the Declaration of Helsinki of the World Medical Association (Simões, Santos, & Biscaia, 2016).

Instruments

To carry out the exploration of the neuropsychological functions of the orbitofrontal cortex, three computerized tasks were performed to assess the functions of vigilance, concept formation, mental flexibility and planning (Ferreira et al., 2015), included in the STIM program by NeuroScan, Inc., with the following settings:

a) Stroop Test (Stroop, 1935), which assesses attentional skills, concept formation, planning and mental flexibility (Fernández-Alcántara, et al., 2016). It involves the successive presentation of 100 verbal stimuli (words denoting four colors, randomly written in the colors they designate or any of the other colors used) with a duration of 100 ms. for each stimulus, an interstimulus interval of 1 s. and a window of response (fraction of time for the subject to produce the answer) of 1 s. There were two alternatives for the presentation of stimuli: The word could be written in the same color that it described (congruent stimuli), in which case the subject had to click the right mouse button, or the word could be written in a different color from the one it designated (incongruent stimuli), in which case it was the left button that had to be clicked. The performance of the task enables the following measures to be obtained: The percentage of correct answers, the number of responses out of time (time outs), the reaction time to congruent stimuli, and the reaction time to incongruent stimuli.
b) The Wisconsin Card Sorting Test (WCST) (Heaton, 1981), which evaluates hypothesis formation, problem solving, the ability to shift cognitive sets, abstraction skills, and cognitive flexibility, in addition to concept formation and planning (Gameiro, Perea, Ladera, Rosa & García , 2017).

This test has been shown to detect neuropsychological dysfunctions involving the dorsolateral prefrontal cortex, such as response inhibition and inflexible behavior.

The difficulty of the task lies in the existence of three different classification criteria (color, shape and number) which are not disclosed to the subject and which will remain the same until 10 correct answers are met, being progressively modified automatically. The program provides visual and auditory feedback which informs the subject if the answer is right or wrong. The measures provided by the test are the number of correct responses, the number of errors and the number of completed categories.

c) The Continuous Performance Test (CPT) (Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956) visual-motor task of sustained attention or vigilance (Moreno-García, Delgado-Pardo, De Rey, Meneres-Sancho, & Servera-Barceló, 2015), consisting of the presentation of 400 stimuli, grouped for analysis into four blocks of 100 stimuli. Each stimulus, consisting of a letter that appears in the center of the screen, was presented with a duration of 50 ms. and an interstimulus interval of 1 s. The task, of a conditioned nature, required the subject to click the right mouse button whenever a particular sequence of letters appeared (P and T, consecutively in this order). The letter P acted as the signal and the letter T as the target stimulus. There were 15 each of the target items (P followed by T) and the foil items (P followed by a different letter), for each block of 100 stimuli.

The measures obtained were the number of correct answers (to target stimuli), commission errors (responses to irrelevant stimuli) and two measures derived from signal detection theory: A measure of sensitivity (A-prime, or the degree of discrimination between signal stimuli and contextual stimuli or "noise", which is higher the greater the discriminative ability), and β or the response criterion adopted by the subject, which represents the degree of prudence-impulsivity in their responses. Low values indicate a risky response pattern, increasing the number of targets and false alarms; and high values indicate a conservative criterion, reducing both the numbers of correct answers and the false alarms). The distinction between A-prime and β separates the factors of attentional capacity from those that are motivational.

Procedure

In all cases, both the patients and the healthy controls agreed to participate by signing a document of informed consent, and they performed the neuropsychological tests in similar and standardized conditions, individually in a laboratory at the Faculty of Psychology at the University of Oviedo (Spain). The inclusion criteria, both in the Chiari group and in the control group, were confirmed by expert practitioners and validated by the specialist neurosurgeon. All patients were selected through the Neurosurgery Service at the Hospital Centro Médico of Asturias (Spain) and the subjects chosen as the healthy controls were randomly selected from a list of volunteers, excluding those whose age was not included in the age range of the Chiari patient group. The healthy controls were also selected through the Hospital Centro Médico. No significant differences were observed in the age, marital status or level of schooling among the people belonging to the two groups, experimental and control.

Data analysis

To compare the results obtained in the neuropsychological tests by the participants belonging to the two groups, a multivariate analysis of variance (MANOVA) was carried out, which enabled us to check for global differences. When Wilks's λ was significant ($p \leq 0.05$), the univariate analyses of variance (ANOVA) aimed to determine the variables in which the groups showed differences. eta^2 was used as an effect size index (Badenes-Ribera, Frías-Navarro, Monterde, & Pascual-Soler, 2015). Values of eta^2 > 0.15 are considered high, and when eta^2 > 0.06 the effect size is moderate. Subsequently, a discriminant analysis was performed to determine the discriminative capacity of each variable. All statistical analyses were performed using SPSS version 15.0 for Windows.

Table 1
Comparison of the scores obtained by the experimental and control groups in the neuropsychological variables

	Chiari I M (SD)	Healthy controls M (SD)	F	p	η^2
Neuropsychological variables					
Stroop Test	85.66 (14.57)	89.79 (15.69)	.742	.394	.019
% correct answers	13.35 (11.06)	6.85 (10.23)	3.725	.061	.089
Time outs	772.57	639.29	5.172	.029	.120
Reaction time to congruent stimuli	(148.03)	(216.29)	5.654	.023	.130
Reaction time to incongruent stimuli	841.01 (92.38)	729.82 (187.61)			
WCST					
Nº of correct answers	46.75 (9.93)	53.9 (8.42)	6.026	.019	.137
Nº of errors	72.45 (12.71)	45.9 (27.42)	15.431	.000	.289
Nº complete(d) categories	4.4 (1.14)	5.2 (1.10)	5.067	.030	.118
CPT					
Nº of correct answers	54.4 (4.66)	55.15 (12.62)	.062	.805	.002
Nº of commission errors	4.39 (10.66)	2.01 (5.30)	.799	.377	.021
Answer criteria: β	.59 (.36)	.60 (.15)	.032	.859	.001
Sensitivity: A prime	.94 (.04)	.95 (.06)	2.571	.117	.063
Reaction time	348.54 (80.23)	312.02 (62.75)	.270	.607	.007

Note: WCST: Wisconsin Card Sorting Test; CPT: Continuous Performance Test. Wilks's value = 3.186, p= .006

Results

As shown in Table 1, the scores on the neuropsychological tests show global differences between the two groups analyzed (Wilks's value: $F = 3.186$, $p = .006$). In the Stroop test, the Chiari patients have a comparatively longer reaction time to both *congruent stimuli* ($F = 5.172$, $p = .029$) and to incongruent stimuli ($F = 5.654$, $p = .023$) compared to the healthy controls. A tendency to respond out of time (time outs) ($F = 3.725$, $p = .061$) is also observed.

In the Wisconsin Test, in comparison with the healthy controls, the Chiari patients had a lower number of correct answers ($F = 6.026$, $p = .019$), and a greater *number of errors* ($F = 15.431$, $p = .000$) and a smaller number of completed categories ($F = 5.067$, $p = .030$). After analyzing the results obtained in the CPT, no significant differences were found in any of the variables.

Discussion

Traditionally, the cerebellum has been considered to be a structure that is essentially involved in the coordination and control of voluntary movements, however, after decades of research, as a result of the findings in neuroanatomy, neuroimaging and clinical neuropsychology, today the cerebellum is directly associated with cognitive processing and emotional control (Schmahmann & Caplan, 2006). The functional heterogeneity of the cerebellum and its influence on different cognitive functions in patients with cerebellar lesions can be explained through diaschisis (Beaton & Mariën, 2010; Starowicz-Filip, Milczarek, Kwiatkowski, & Bętkowska-Korpała, 2013), although there is no conclusive evidence regarding the pathogenic mechanisms to explain the deficits in cognitive functions presented after cerebellar lesion (Timmann & Daum, 2014), and which are similar to those that are evident after frontal lesions with additional deficits of different degrees in visual-spatial, social cognition, memory and language functions (Bostan, Dum, & Strick, 2013; Schmahmann, 2010). In this regard, patients with Chiari Type I show cognitive deficits that could be interpreted as a consequence of the cerebellar alteration, however, the pathophysiological process of CM I includes extra-cerebellar structures, making it difficult to attribute the cognitive deficits solely to cerebellar dysfunction. The aim of this study is to understand the relationship between the cerebellum and the neocortex with regards to the executive functions, and also to determine whether alterations in these cognitive functions are a key pathophysiological component of CM I.

Different studies on the cognitive functions altered after a cerebellar lesion resemble those occurring after frontal lobe lesions, especially those affecting the prefrontal dorsolateral region (Stern & Prohaska, 1996). Alterations in functions such as planning, abstract reasoning, perseverance and self-regulation are part of the executive functions described by Luria and would be included in a dysexecutive syndrome (Baddeley & Wilson, 1988). As indicated above, Schmahmann & Sherman (1998) and Schmahmann (2004, 2013) propose cerebellar cognitive affective syndrome (CCAS) which includes alteration of the executive functions. The cases included originally by Schmahmann & Sherman (1998) describe patients with cerebellar lesions that are shown in the head MRI at the level of the cerebellum. In cases of Chiari I Malformation, these patients have structures without signal alteration in their anatomy, although part of it (the cerebellar tonsils) has migrated at least 5 mm towards the spinal canal. There is evidence that substantiates the hypothesis that frontal hypofunction observed in patients with CM I could be associated with cognitive deficits, which may explain the dysfunctions found in the Stroop Test (Allen et al., 2014). In our study, we observed that the Chiari patients have a longer reaction time to *congruent* and *incongruent stimuli* than the healthy controls, as well as a tendency to respond out of time. These results could be indicative of an impairment/alteration of the inhibition processes (Neau, Arroyo-Anllo, Bonnaud, Ingrand, & Gil, 2000) and the self-control characteristics of the prefrontal executive functions (Tirapu et al., 2011).

In the Wisconsin Test, the Chiari patients performed poorly; not only did they obtain fewer correct answers and more errors, but they also completed fewer categories. These results suggest an alteration in the attention span and in maintaining the course of thought and action, as well as the basic mechanism of discrimination between relevant and irrelevant stimuli, which would explain the difficulty in organizing stimuli correctly, generating concepts and solving problems (Abel et al., 2005; Ravizza & Irvy, 2001). These results suggest fundamentally neurocognitive deficit in the prefrontal cognitive functions (measured by WCST and Stroop tasks), and not so much in attention (measured with CPT).

In conclusion, the results obtained provide evidence of possible deficits or abnormalities in patients with Chiari Type I in the prefrontal neuropsychological functions of self-regulation of behavior, self-control and, in general, cognitive executive functions. These anomalies could represent a characteristic pattern in Chiari Type I disease and help to explain the role of the cerebellum in the cognitive functions by virtue of its connections with the frontal and prefrontal areas of the cortex.

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