Research article

Anxiety and depression in Chiari malformation

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Abstract

There are few studies that explore the involvement of the cerebellum in the affective area. This study aims to evaluate the affective component and, specifically, the emotional states of depression and anxiety associated with the Chiari malformation, controlling perceived pain. This study included a Chiari group and two control groups, one healthy, the other suffering from Myasthenia gravis, which exhibits a physical component without cerebellar impairment. Each participant completed the Hospital Anxiety and Depression Scale and the Numeric Pain Rating Scale. Scores were significantly higher for the anxiety variable in the Chiari group, either when compared to the control group or the group affected by Myasthenia gravis-controlling the level of headache. The results obtained support previous studies in which the important contribution of the cerebellum to emotional regulation was emphasized.

Keywords

cerebellum, Chiari malformation, depression, anxiety, pain, observational descriptive study.

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1. Introduction

The cerebellum has historically been regarded as one of the brain structures essential for coordination of movement. In 1899, Babinski [1] described a cerebellar motor syndrome, which among other problems includes a series of symptoms such as ataxic gait, dysarthria, and oculomotor abnormalities. Recently, different studies have provided evidence that the presence of cerebellar degeneration or stroke may involve cognitive deficits beyond motor impairment, including the ability to form concepts and other language disorders [1, 2], impairment in executive functions [3], and visuospatial deficits [4], accompanied in many cases by a regressive personality, and emotional lability or dramatic mood swings. Despite these findings, there are few studies that explore cerebellar involvement in non-motor behaviors. One of the most revealing studies was Schmahmann and Sherman's [5] study of 20 subjects with various disorders localized to the cerebellum, such as stroke in the anterior inferior cerebellar, posterior inferior cerebellar, or superior cerebellar arteries, and post-infectious cerebellitis and cerebellar cortical atrophy. The study's findings revealed the existence of a cerebellar cognitive affective syndrome described by Schmahmann and Sherman [5] as characterized by the following: (a) Disturbances of executive function, including deficient planning, set-shifting, abstract reasoning, working memory, and decreased verbal fluency, (b) Impaired spatial cognition, including visuospatial disorganization and impaired visuospatial memory, (c) Linguistic difficulties, including dysprosodia, agrammatism, and mild anomia, and (d) Personality change, characterized by flattening or blunting of affect, and disinhibited or inappropriate behavior. Aberrant modulation of behavior and personality due to posterior lobe lesions involve midline structures. Personality changes include flattening or blunting of affect, disinhibited behaviors, such as over-familiarity, flamboyance, impulsive actions, humorous but inappropriate and flippant comments, regressive, childlike behaviors, and obsessive-compulsive traits.

Neuropsychiatric manifestations described by patients with cerebellar disorders in relation to emotional control include on the one hand, a series of exacerbated positive symptoms such as impulsiveness, disinhibition, lability, unpredictability, incongruous feelings, pathological laughing and crying, agitation and panic, and, on the other hand, negative symptoms such as obsessional thoughts, anergy, anhedonia, sadness, hopelessness, dysphoria, anxiety, and depression. Remote episodic and semantic memories were preserved, and new learning was only mildly affected. Other cortical phenomena were largely absent, such as, for example, aphasia, apraxia and agnosia [6–8].

Although experiments have shown that the cerebellum is a key structure in emotional regulation, there are few studies that explore the involvement of the cerebellum in the area of affect. After assessment of 43 young adults who had recovered from isolated cerebellar or brainstem infarcts, Hoffmann & Cases [9] observed impairments in disinhibition, executive function, emotional intelligence and apathy tests. Other case studies have noted consequences of a cerebellar stroke may include marked alteration of personality with dysphoria, disinhibition, affective indifference to family, memory loss, panic disorder, agitation, anxiety, and episodes of crying [10, 11].

A study by Turner et al. [12], that employed positron emission tomography, attempted to clarify the effects of cerebellar lesions on brain circuits subserving emotional experiences by examining six patients suffering from cerebellar stroke and a control group, while they responded to emotion-evoking stimuli selected from the International Affective Picture System [13]. Both the clinical and control groups showed a similar response to stimuli evoking the

emotion of fear. The results of that study suggested the cerebellum is a node in the neural network that underlies the subjective experience of emotion.

The systematic review of the literature on the affective component of the cerebellar cognitive affective syndrome by Wolf *et al.* [14] is also noteworthy. After analyzing 11 studies, the authors concluded that subjects that exhibited cerebellar pathology had higher depressive and anxiety scores in some but not all the studies. The authors highlighted tentative evidence supporting the role of the cerebellum in the affective syndrome in patients with cerebellar damage. Furthermore, they emphasized the limitations of the studies, among which they included the limited number of studies that employed a control group, and the lack of demarcation of the location of the cerebellar injury. The authors emphasized the need for standardized and sensitive evaluation measures to detect changes at an emotional and behavioral level. Finally, they stressed that future studies should employ comparison groups that include patients with other disorders or brain injuries. The affective deficits that follow acute cerebellar lesions need to be established through larger, prospective and longitudinal studies [5].

Several authors have reported cognitive and emotional changes in people suffering from diseases that effect the functioning of the cerebellum, specifically type 3 spinocerebellar ataxia (Machado Joseph disease), which also involves limitations in executive functions, emotional instability, impulsivity and depression [15–17]. In another study of patients that exhibited Friederich's ataxia, it was found that scores on the depression inventory were significantly higher in patients than controls, but that depression did not account for group differences in cognitive performance [18].

Mestres *et al.* [19] conducted one of the few studies that evaluate quality of life in 67 subjects with Chiari I malformation, but in the absence of a control group. Chiari disorders are a malformation of the cerebellum and brainstem with varying degrees of cerebellar migration through the foramen magnum into the cervical canal, described by Dr. Hans Chiari in 1891 [20]. Chiari I malformation (ACM-I) consists of a herniation of the cerebellar tonsils into the foramen magnum [21]. Mestres *et al.*'s [19] quality of life study focused especially on the analysis of the presence of anxiety or depression. Their results showed that 86% of patients had moderate or high anxiety, while in 25% of cases depressive symptoms were noted. The presence of depressive and anxious symptoms in this group is also reflected in the two case studies reported by Klein *et al* [22]. The importance of these variables is such that they can, in turn, influence the cognitive performance of those affected by Chiari, including working memory or processing speed [23]. There is also an interesting review about the cerebellar role in cognition and emotion [24]. Among the limitations of this research, it is important to note the use of assessment tools for anxiety and depression do not take into account the physical component of the disease and its potential overlap with psychological symptoms, such as in the case of Beck's Anxiety and Depression Inventories [25]. Headache is one of the most common symptoms among the manifestations of Chiari malformation (15-98% of the patients), including sub-occipital, occipital, and neck pain described as a heavy, crushing or pressure like sensation radiating to the vertex, behind the eyes, to the neck and shoulders, and cough headache, aggravated by the Valsalva maneuver but relieved by craniectomy [26–29]. Individuals with chronic pain commonly have mood disorders which lead to a poorer quality of life. These include affective, generalized anxiety, substance-use related, and somatoform disorders. The prevalence of depression is higher among chronic pain patients and depressed patients complain of more pain symptoms than those who are not depressed. Patients with chronic pain also have a higher prevalence of anxiety disorders and these have been related to somatic complaints such as pain [30–33].

This study aims to evaluate the affective component, more specifically, the emotional states of depression and anxiety associated with the Chiari malformation. The presence of depression and anxiety in a disorder linked so closely with the cerebellum leads to a question of whether its genesis lies either more in an adaptive response as a result of coping with the disease or whether the explanation is mediated by injury or impairment of the functioning of brain structures involved in the disorder. The influence of the perception of headache pain in the depressive and anxious states of the patients will be taken into account. To address this issue, as highlighted by Wolf *et al.* [14] within the limitations of previous studies the current study included control groups of both healthy subjects and subjects suffering from another disease, Myasthenia gravis (MG), which has a physical component, but no cerebellar impairment. MG is an autoimmune disorder of neuromuscular transmission that is characterized by an increased fatigability of voluntary muscles [34]. An increased incidence of psychiatric disorders, such as depression and anxiety have also been noted in patients with MG, due to the expected consequences of a chronic but unpredictable neuromuscular disease that involves weakness of breathing, swallowing, talking, and limb and eye movements [35–37]. Both diseases are physical disabling, but MG is an organ-specific autoimmune disease caused by an antibody-mediated assault on muscle nicotinic acetylcholine receptors at the neuromuscular junction, whereas, Chiari is a malformation of the cerebellum and brainstem with varying penetration through the foramen magnum into the cervical canal. In general, MG has no cerebellar impact. This study explores the possible implication of the cerebellum in altered mood states.

2. Methods

2.1. Participants

The Chiari clinical sample consisted of 19 patients diagnosed with Arnold-Chiari malformation (15 males, 4 females, mean age 48.68 years, SD = 9.77). Of these 19 subjects (17 with subtype I and 2 with subtype II), 13 had Chiari malformation and 6 also suffered from syringomyelia. 31 clinical patients suffered from MG (10 males, 21 females, average age 50.25 years, SD = 13.29).

Inclusion criteria for both groups of subjects were: (1) Confirmed Chiari or MG diagnosis, (2) Age >18 years, and (3) Completion of a signed informed consent form. Patients were excluded if they suffered from any psychiatric (DSM IV-TR) or neurological disorder other than Chiari or MG, any head trauma, or any severe visual limitations.

The healthy control group consisted of 20 subjects (16 males, 4 females). They averaged 51.95 years of age (SD = 10.43). Some controls were recruited from adult education courses at the University of Deusto (Basque Country). Their inclusion criteria included: (1) Age >18 years, (2) Completion of a signed informed consent form, and (3) Ability to use a computer. As with the clinical groups, healthy participants were excluded if they suffered from any psychiatric or neurological disorder, head trauma, or severe visual limitations.

There were no statistically significant differences between the three groups in terms of gender ($X^2 = 1.25$, $df = 2$, $p = 0.54$). Each

participant completed the task in Spanish and gave their informed consent. All subjects volunteered to complete the study without compensation. The study was conducted in compliance with ethical research standards approved by an Ethics Committee. X^2 is the Chi squared, df is the degree of freedom , SD is the Standard Deviation.

2.2. Apparatus

The Hospital Anxiety and Depression Scale (HADS) was developed in the early 1980s as a tool to identify emotional disorders in non-psychiatric patients within a hospital setting [38]. The scale is self-administered and consists of 14 items split across anxiety and depression sub-scales, each with a four-point ordinal response format. The test has no items relating to somatic symptoms that might confuse the diagnosis of subjects who may also have physical illness, thus reducing their sensitivity in screening for depression or anxiety. The HADS has been shown to exhibit adequate diagnostic accuracy. The authors recommend that a score above 8 on an individual scale should be regarded as a possible case and a score above 10 a probable case of anxiety or depression. A recent meta-analysis study reported that, using a score of 8 or more as the cut-off, the HADS depression scale yielded 82% sensitivity and 74% specificity in the detection of major depressive disorders; and the anxiety scale yielded 78% sensitivity and 74% specificity in the detection of a generalized anxiety disorder. It is the third most used self-report screening test with an annual citation rate of approximately 1333 [39, 40]. In this study, the Spanish version of HADS was employed. This adaptation was analyzed for a group of 379 healthy Spanish students and 182 student questionnaires. This version showed both an optimal internal consistency and test-retest reliability (>0.70), and a good correlation with other anxiety and depression sub-scales [41].

The Numeric Pain Rating Scale (NPRS) [42] is a unidimensional measure of pain intensity in adults including those with chronic pain. It is a segmented numeric version of the visual analog scale in which a subject selects a number in a horizontal bar or line (0–10) that best describes the intensity of his/her pain. The Chiari sample was asked about the perception of headache on a scale with an 11-point numeric scale ranging from '0' representing one extreme (e.g. "no pain") to '10' representing extreme pain (e.g. "pain as bad as you can imagine"). The NPRS can be administered either verbally or self-administered and is a valid and reliable scale for the measurement of pain intensity. High test–retest reliability has been observed in both literate and illiterate patients with rheumatoid arthritis ($r = 0.96$ and 0.95, respectively) before and after medical consultation. For construct validity, the NPRS has been shown to be highly correlated with the Visual Analogue Scale in patients with rheumatic and other chronic pain conditions with correlations range from 0.86 to 0.95 [43].

2.3. Procedure

During the first period, data from subjects with the Arnold Chiari condition and control group one were obtained. The clinical sample consisted of patients in The Friends of Arnold Chiari National Association (Asociación Nacional de Amigos de Arnold Chiari, ANAC) and the Spanish Association of Myasthenia (Asociación Española de Miastenia, AMES). The control group was composed of adults taking courses within the University of Deusto who wanted to take part in the study and who complied with the sociodemographical characteristics required by the study. All the participants were fully informed about the study and gave informed consent. The experiment was conducted in a silent room at one of two different sites: University of Deusto (Basque Country) and the Reference Centre for Rare Diseases in Spain. After the experimenter provided verbal instructions, the participants completed a sociodemographic questionnaire and the HADS Test. The NPRS was applied to Chiari subjects to control for the influence of headache on anxiety and depression scores. The group of subjects with MG did not completed this assessment as the headache variable was irrelevant. The entire protocol was administered individually in one approximately 15 minute session per subject and in the same order for all subjects. There was no economic reward for participation. Ethical aspects such as assuring data confidentiality, not causing any harm to those taking part in the study, and explaining the reasons and implications of the study were considered.

2.4. Statistical analysis

Prior to data analysis, all variables were checked for normality using the Kolmogorov-Smirnov test ($p > 0.05$). All data were non-normally distributed; therefore, non-parametric statistics were used. Mann-Whitney U and Kruskal Wallis tests were used to compare group mean values and correlational analysis was employed to explore the association between variables. All significance levels were calculated using two-tailed tests, and the significance level was set at 0.05. Data were analyzed with the SPSS statistical program, version 19.

3. Results

Initially, the mean scores of both groups for anxiety and depression are described, where a score higher than 11 in the HADS questionnaire, was considered to indicate a possible case of anxiety or depression. The average score obtained for the anxiety sub-scale of the control group was 4.60 (SD = 4.03), whereas, for the group of subjects with Chiari malformation, it was 12.11 (SD = 5.31), with 58% of these subjects reporting a level of anxiety higher than 11. The average score for MG subjects was 7.90 (SD = 4.25). In relation to the depression sub-scale, the control group exhibited a mean of 1.7 (SD = 1.9) in comparison with the Chiari subjects who gave a mean of 8 (SD = 4.32) and the MG group with 5.81 (SD = 4.04). In this sub-scale, 32% of the subjects with Chiari malformation exceeded a score of 11. If the scores on depression and anxiety between the two evaluated diseases are compared, the group affected by Chiari malformation obtained the highest scores Table 1.

Table 1. The scores on depression and anxiety between the two evaluated diseases

		n	Mean	Standard deviation
HAD Anxiety	Control	20	4.60	4.03
	Chiari	19	12.11	5.31
	Myasthenia	31	7.90	4.25
HAD Depression	Control	20	1.70	1.94
	Chiari	19	8.05	4.32
	Myasthenia	31	5.81	4.04
HAD Total	Control	20	6.250	5.72
	Chiari	19	20.158	8.93
	Myasthenia	31	13.935	7.26

These differences in scoring were also reflected at a statistical level through a Kruskal Wallis analysis. This analysis revealed statistically significant differences between the total HADS scores for the three groups [H (2) = 24.35, $p = 0.00$], both for the level of anxiety [H (2) = 19.94, $p = 0.00$] and for the level of depression [H (2) = 25.07, $p = 0.00$]. H is the Kruskal Wallis statistic.

To obtain a more detailed analysis of differences, post hoc Bonferroni correction tests were applied. Through this test, it can be unequivocally concluded that significantly higher scores were obtained for the anxiety variable in the Chiari group, when compared to both the control group and the MG affected group. However, in the case of the depression sub-scale, no statistical differences between the two clinical groups were found. These results are also supported by the Mann Whitney U-test performed on the data from these groups. This analysis revealed statistically significant differences for the anxiety variable with a moderate effect size ($U = 169.5$, $p = 0.012$ $r = 0.35$), but no statistically significant difference between groups for the depression scale ($p = 10$). U is the Mann Whitney.

To analyze the association between mood states and pain in the Chiari group, a correlation analysis was performed. There is no significant correlation between the NPRS and Anxiety or Depression, so there is no correlation between perception of pain and the evaluated mood states.

Finally, two variables associated with the Chiari diagnosis were analyzed, first, the presence of syringomyelia and secondly, the presence or absence of the surgical operation specific to this malformation. In both cases, answers given for the two HADS questionnaire sub-scales of anxiety and depression were distributed similarly among the categories analyzed. That is, for the analyzed sample, there were no significant differences between subjects affected by Chiari that had received surgical intervention and those who were unoperated ($p > 0.05$) or between those with syringomyelia and those without this comorbidity ($p > 0.05$).

4. Discussion

The aim of this study was to analyze the presence of anxiety and depression in patients with Chiari malformation, while controlling for the effect of headache. The results indicate that the Chiari group exhibited statistically significant differences in their scores for both the anxiety and depression variables when compared to the control group. However, when these variables were compared to those of subjects affected by MG, the patients with Chiari malformation exhibited significantly higher scores for the anxiety variable, but not for the depression variable. One of the aims of this study is to determine whether the Chiari malformation that leads to descended cerebellar tonsils and subsequent brainstem and cervical spine area compression, causes chronic pain in these patients. Results showed that any association between anxiety scores and pain is not significant, so anxiety can not be explained by headache in the Chiari sample. This confirms results obtained in similar studies of people with Chiari malformation in which moderate or high levels of anxiety were obtained in 86% of the studied sample, compared to 25% of subjects reporting moderate or severe depressive symptoms [19]. A study by Allen et al. [23] also reported this difference, finding higher scores for the anxiety variable than for the depression variable when a group of patients with Type I Chiari were compared with a control group. Such results, however, contrast with the findings of Leroi et al. [44], which compared subjects suffering from cerebellar degenerative disorders with healthy subjects and individuals with Huntington's disease. Among their findings, it can be highlighted that there were no significant differences for the anxiety variable between the two groups with neurological disorders.

Converging evidence suggests that the cerebellum may play a role in emotional regulation, including anxiety disorders. The cerebellum maintains a large density of corticotrophin-releasing hormone receptors and cannabinoid receptors [45].

The results obtained in the present study show the need to propose alternatives to successfully compensate for the deficits that may arise from cerebellar disorders. In this sense, it is essential to educate regarding the problems a cerebellar injury may cause, stressing that the consequences are an outcome of brain injury. Likewise, it is essential to motivate both those affected and their families to empower patients in their recovery. The existence of psychological disorders in these patients has to be considered through a psychosocial evaluation process so as to achieve an increase in the different domains of quality of life of those affected, such as the perception of pain [46]. It is beneficial for families to know that the non-motor consequences of a cerebellar disorder, such as depression or anxiety, may not be only a psychological reaction to the disorder, but may also be a part of the disorder itself. The detection of cerebellar cognitive affective syndrome and especially its involvement at an emotional level, can facilitate cognitive and behavioral therapeutic intervention to help those affected, and their environment, to face the non-motor consequences of the disease and to recover healthy emotional and cognitive functioning [47]. Furthermore, other types of intervention could be considered for people with cerebellar impairment that may involve the use of drugs to treat associated behavioral and neuropsychiatric symptoms, or other techniques, such as transcranial magnetic stimulation of the cerebellar limbic area, as in the case of people with schizophrenia [48].

This study had some limitations, the first was related to the relatively small sample size. However, the Chiari malformation is an uncommon disease, and this study included one of the largest cohorts of Chiari malformation patients in the literature being compared to a control group of healthy individuals and a clinical group of people suffering from a neuromuscular disease without cerebellar impairment. Another limitation is that only the affective component of the cerebellar cognitive affective syndrome was assessed. Therefore, it is not clear if subjects really exhibited the syndrome or not. Though findings suggested the Chiari group had a significantly higher score for the anxiety variable, as compared with MG and control groups, it is hard to determine whether the difference is due to psychological reaction towards the illness or to a so called cerebellar cognitive affective syndrome. Thus, future studies should include neuropsychological and/or neuroimaging data with structural scans that demonstrate that the Chiari group actually exhibits the syndrome. Further research should also consider the effects of medication, the type of Chiari malformation, and the exact location of the lesion in the cerebellum. Moreover, it would be useful to perform the study using a more extensive evaluation protocol focused on emotional variables to compare the results obtained with the applied questionnaire.

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Conflict of Interest

The authors declare no conflict of interest.

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