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Is Addenbrooke's Cognitive Examination III Sensitive Enough to Detect Cognitive Dysfunctions in Patients with Focal Cerebellar Lesions?

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Abstract

Objective: The main aim of the study was to evaluate whether the available brief test of mental functions Addenbrooke's cognitive examination III (ACE III) detects cognitive impairment in patients with cerebellar damage. The second goal was to show the ACE III cognitive impairment profile of patients with focal cerebellar lesions.
Method: The study sample consisted of 31 patients with focal cerebellar lesions, 78 patients with supratentorial brain damage, and 31 subjects after spine surgery or with spine degeneration considered as control group, free of organic brain damage. The ACE III was used.
Results: Patients with cerebellar damage obtained significantly lower results in the ACE III total score and in several subscales: attention, fluency, language, and visuospatial domains than healthy controls without brain damage. With the cut-off level of 89 points, the ACE III was characterized by the sensitivity of 71%, specificity of 72%, and accuracy of 72%. The cerebellar cognitive impairment profile was found to be "frontal-like" and similar to that observed in patients with anterior supratentorial brain damage, with decreased ability to retrieve previously learned material and its preserved recognition, impaired word fluency, and executive dysfunction. The results are consistent with cerebellar cognitive affective syndrome.
Conclusions: The ACE III can be used as a sensitive screening tool to detect cognitive impairments in patients with cerebellar damage.

Keywords: Cerebellum; Cognitive functions; ACE III

Key points

- Is Addenbrooke's cognitive examination (ACE III) sensitive enough for assessing cognitive functioning of patients with cerebellar damage?
- Our study determined the cut-off point in the ACE III total score and the ACE III particular cognitive domains for individuals with cerebellar lesions, in comparison to subjects without organic brain damage and patients with supratentorial brain lesions.
- The cerebellar cognitive profile is similar to that observed in patients with frontal lobe damage, characterized by decreased ability to retrieve previously learned material, impaired word fluency, and executive dysfunctions.

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- Confirmation of the usefulness of the ACE III in cerebellar patients has a practical value and enriches the practice of clinical neuropsychologist in the department of neurosurgery and neurology.

Introduction

The present-day discussion over the role of the cerebellum in cognition no longer focuses on "whether or not" the cerebellum is involved in cognitive functioning, but "how" the cerebellum participates in cognitive processes (Koziol et al., 2014). Schmahmann and Sherman's (1998) idea of "cerebellar cognitive affective syndrome" (CCAS) concerning the presence of executive dysfunctions, visuospatial impairments, linguistic deficits, and affective dysregulation in patients with cerebellar lesions has been investigated and widely confirmed in several studies. A growing body of scientific research suggests that damage limited to the cerebellum is associated with deficits in cognitive processes, such as, phonological short-term memory (Ph-STM) (Timmann & Daum, 2007), episodic memory (Andreasen et al., 1999), attention and processing speed (Beebe et al., 2005; Steinlin et al., 2003), executive functions including planning and sequencing (Levisohn, Cronin-Golomb, & Schmahmann, 2000), visuospatial functions (Starowicz-Filip, Chrobak, Milczarek, & Kwiatkowski, 2017), and word fluency (Arasanz, Staines, Roy, & Schweizer, 2012).

Over the past few decades, research has established that the cerebellum is involved in executive functions, planning, inhibition, and flexibility (Bull, Liossi, Peacock, Ming Yuen, & Kennedy, 2015; Clark, Semmel, Aleksonis, et al., 2021; Riva, Cazzaniga, Esposito, & Bulgheroni, 2013). Moreover, many authors focus on cerebellar involvement in verbal working memory (WM) (Marvel & Desmond, 2010; Ziemus et al., 2007), with neuroimaging studies, which report cerebellar activation during verbal WM tasks (Chein, Fissell, Jacobs, & Fiez, 2002; Gerton et al., 2004). This clinically observed "frontal like" profile of cognitive dysfunctions after cerebellar lesions can be explained by the existence of cerebellar-subcortical–cortical pathways between the cerebellum and prefrontal cortex (the fronto-ponto-cerebellar tracts and the cerebello-thalamo-frontal tracts).

The role of the cerebellum in the regulation of verbal WM has typically been interpreted with Baddeley's model. In this theoretical framework, the verbal slave system (phonological loop) stores information in a phonological store and prevents its decay by an active rehearsal mechanism akin to "inner-speech" (articulatory rehearsal) (Ben-Yehuda, Guediche, & Fiez, 2007).

Ben-Yehuda et al. (2007) rely on three theoretical mechanisms that may explain the role of the cerebellum in verbal WM. Firstly, the cerebellum takes part in an articulatory rehearsal mechanism in phonological loop. The activity in the cerebellum together with the activity in cortical frontal regions will persist across a delay interval, during which rehearsal refreshes decaying verbal information in the phonological store (Ben-Yehuda et al., 2007). The second explanation is error-driven adjustment model. Fluid movements, controlled by the cerebellum, are also important for normal speech. To explain both the fluency and the absence of errors in speech, many models of speech production have incorporated a monitoring process that detects errors and adjusts the planned articulation prior to its execution. The cerebellum is the one important component of this monitoring process. Cerebellar dysarthria correlates with performance on a verbal span-matching task; dysarthria influences the inner-speech mechanisms during verbal WM (Ben-Yehuda et al., 2007). Finally, the last model concluded that the cerebellum is important for the temporal organization of internal speech (Ben-Yehuda et al., 2007). Moreover, the results of Ailion's study (Ailion et al., 2020) provide empirical support for the theory that the cerebellum and its frontal white matter connections are implicated not only in the phonological loop of the verbal WM, but more specifically correlate with auditory attention span.

The earlier-mentioned cognitive processes: executive functions, WM, and auditory attention span secondarily condition a whole range of other cognitive domains, such as memory and learning a new material, word fluency, or even visuospatial processes (Ailion et al., 2020). The cerebellum is considered as a modulator, rather than a generator of cognitive processing (Schmahmann, Guell, Stoodley, & Halko, 2019).

However, because cerebellar damage usually results in mild cognitive impairments, much more subtle than these observed in cortex lesions (Ferrari et al., 2018), it is interesting whether the cerebellar cognitive dysfunctions could be detected by the neuropsychological screening tools commonly used in cortex dysfunction examination.

One very promising screening tool for cognitive processing is Addenbrooke's cognitive examination (ACE III), developed by Hodges and Larner (2017). This extended cognitive screening technique composed of tests of attention, orientation, memory, language, visuo-perceptual, and visuospatial skills was originally designed to detect dementia, and to differentiate Alzheimer dementia from fronto-temporal dementia (Mathuranath, Nestor, Berrios, Rakowicz, & Hodges, 2000). The ACE III has a more extended assessment scale (from 0 to 100 points) than other standard screening tests, such as the montreal cognitive assessment (MoCA) or mini-mental state examination (MMSE) (both from 0 to 30 points), therefore, it allows for a more detailed examination. Many studies confirmed the statistical correlation of ACE III results with other neuropsychological tests scores,

such as the Wechsler Adult Intelligence Scale-Digit Scale, the Rey Auditory Verbal Learning, the Sydney Language Battery, the Rey-Osterrieth Complex Figure Test, and the Frontotemporal Dementia Functional Rating Scale (Mathuranath et al., 2000; Matias-Guiu, Cortés-Martínez, Valles-Salgado, et al., 2017), suggesting the sufficient validity of the ACE III.

Given that the ACE III not only provides the clinician with a cut-off point, but also shows an estimated cognitive profile of the patient (Matias-Guiu et al., 2017), some researchers postulate that it could be successfully used for assessing cognitive functioning in groups of subjects other than dementia (Bruno & Schurmann, 2019). The utility of the ACE III in the detection of cognitive impairment has already been checked in patients after stroke (Lees et al., 2017), patients with multiple sclerosis (Figlus, Obrembska, Miller, & Głąbiński, 2018), and brain tumors (Cherkil, Panikar, & Soman, 2017; Kerrigan, Rooney, & Grant, 2011; Tymowski, Kaspera, Metta-Pieszka, Zarudzki, & Ładziński, 2018). These studies provided promising results regarding the possible extension of the ACE III application.

In the present study we intended to determine (1) whether the ACE III could be a sensitive enough screening tool, to detect cognitive dysfunctions in patients with focal cerebellar damage; (2) what is the cognitive profile of patients with focal cerebellar damage, in particular which cognitive domains, measured with the ACE III are preserved and which are impaired; and (3) whether this cognitive profile differs from that observed in patients with extracerebellar, supratentorial brain damage.

We hypothesized that the ACE III total score of patients with focal cerebellar damage may be lower than the ACE III total score of healthy controls. Based on the research on the role of the cerebellum in the regulation of particular cognitive domains, we assumed that patients with cerebellar lesions might obtain lower results in the following ACE III subtests: fluency subtest, attention (especially in serial subtracting as a measure of WM), visuospatial functions, and memory. Based on previous studies showing the significant role of the cerebellar-frontal connections in the regulation of cognitive functions, we assumed that the cerebellar patients' cognitive profile would be more similar to that observed in patients with frontal supratentorial brain tumors than to patients with tumor located in the posterior parts of the brain.

Materials and Methods

Participants

Three groups of participants took part in the present study: (1) patients with cerebellar lesions; (2) patients with supratentorial brain lesions; and (3) subjects after spine surgery or with spine degenerative disease, considered as control group, free of organic brain damage. The subjects were recruited prospectively form the neurosurgery ward, rehabilitation, clinic and outpatient care. In case of cerebellar and supratentorial lesion groups, the lesion location was determined by the radiologist, based on magnetic resonance imaging (MRI) results. The inclusion criterion for the cerebellar lesion group was focal cerebellar damage (tumor, stroke, or vascular malformation), whereas the exclusion criteria were presence of extracerebellar brain damage and psychiatric illness. The inclusion criteria for the supratentorial lesion group were the presence of focal lesion in the supratentorial part of the brain, whereas the exclusion criteria were the presence of neurodegenerative disorders and psychiatric illness.

All participants signed an informed written consent to the assessment in line with the Declaration of Helsinki. The study was approved by the local Ethics Committee.

The cerebellar lesion group. The cerebellar lesion group consisted of 31 patients (17 women and 14 men, mean age 51.51, $SD = 16.93$, age range 20–76); among them 13, were diagnosed with left-sided cerebellar lesions, 15 with right-sided cerebellar lesions, and 3 with isolated vermis damage (based on MRI results). In this group, there were 18 patients with cerebellar tumor, 7 patients after cerebellar stroke, 2 patients with posttraumatic hematoma, and 4 patients with cerebellar arteriovenous malformation. None of the cerebellar patients had cerebellar atrophy.

Among patients with cerebellar tumors, there were, seven patients with metastatic tumors, five patients with astrocytoma WHO 1, two patients with meningioma WHO 2, two patients with medulloblastoma WHO 4, one patient with glioblastoma multiforme WHO 4, and one patient with ependymoma WHO 1. The neuropsychological examination was made after neurosurgery and resection of the tumors. The mean time from cerebellar tumor resection or stroke was 4.27 months. Among the cerebellar lesion patients, three had hydrocephalus and needed shunting. One patient was operated due to the cerebellar tumor in childhood. None of the patients had hearing difficulties. Only two patients had visual problems; nine patients (29%) presented slight problems with emotions, being more depressed, irritable, and impulsive, with less criticism of behavior (observation made during the clinical interview made by clinical neuropsychologist).

The supratentorial lesion group. The supratentorial lesion group consisted of 78 subjects (35 women and 43 men; mean age 56.90; *SD* =16.51; age range 20–80); among them, 28 were diagnosed with frontal brain tumors, 18 with temporal brain tumors, 15 with parietal brain tumors, and 9 with occipital brain tumors. In case of eight patients, lesions were extensive and included both the anterior and posterior part of the cerebral hemisphere (based on MRI results). All patients underwent brain tumor surgery.

All patients with focal brain damage were recruited from the Neurosurgery Department and from the Rehabilitation Centre. In case of the cerebellar patients, extra-cerebellar pathology seen in an MRI examination was an exclusion criterion.

The control group. Subjects after spine surgery, as well as subjects with spine degenerative disease, were considered as a control group. This group, composed of 31 subjects (11 women and 20 men; mean age 57.67; *SD* = 13.26; age range 24–83), was recruited from the Rehabilitation Department. The exclusion criterion was a history of neurological and psychiatric illness. The control subjects were matched with regard to age, sex, and education level with patients with cerebellar damage. There were no statistically significant differences in age, gender, and education level between groups (all p values $> .05$).

Method

The ACE III (Hodges & Larner, 2017) is an extended cognitive screening instrument for an early detection of cognitive impairment, initial differential diagnosis of dementia syndromes, and monitoring of disease progression. As previously described, the ACE III is composed of five cognitive domains: attention, memory, language, verbal fluency, and visuospatial abilities. Attention domain (18 points) is tested by asking the patient about the date and current location, repeating back three words, and serial subtraction (Bruno & Schurmann, 2019). Memory domain (26 points) is tested by asking the patient to recall three words, previously repeated, coding and recalling the name and address of a person and recalling widely known surnames from the historical facts or from the politics. Fluency domain (14 points) is tested by asking the patient to list as many words, as they can think of, starting with a specific letter, within 1 min (phonemic fluency), or naming as many animals, as they can in 1 mi (semantic fluency). Language domain (26 points) is tested by assessing speech comprehension: the patient is asked to complete a set of commands, such as "place the paper on the pencil." Graphomotor abilities are also assessed by writing two grammatically complete sentences. Repetition and articulation are checked by repeating several polysyllabic words. Confrontational naming is assessed by naming objects shown in 12 drawings and by answering contextual questions about some of the objects. Lexia is assessed by reading words with irregular sound-spelling correspondence. Finally, visuospatial functions (16 points) are tested by asking the patient to copy two diagrams (cubes), to draw a clock face with the hands set at a specified time, to count a set of dots, and to recognize four fragmented letters (visual gnosis) (Bruno & Schurmann, 2019).

The examination takes about 20 min to complete and is conducted by a psychologist. The total score of the ACE III is based on the maximum score of 100, with higher scores indicating better cognitive functioning. The index study of the ACE III demonstrated high sensitivity and specificity, with cut-offs recommended as follows: 88 (sensitivity =1.0; specificity = 0.96) and 82 (sensitivity = 0.93; specificity =1.0). The ACE III may be used by physicians and psychologists as either a stand-alone cognitive screening or an introduction to a more in-depth neuropsychological assessment.

Procedure

All participants were tested individually by a clinical neuropsychologist during one session. All participants were informed about the possibility of stopping the testing or taking a break if it became too demanding. All test instructions were carefully explained.

Statistical Analysis Plan

Categorical variables were expressed as counts and percentages. Empirical distribution of continuous variables was described using median and quartiles. Associations between continuous variables were summarized by Spearman's rank correlation coefficient. A p value less than .05 was considered a statistically significant result. The comparison of groups was made using the Kruskal-Wallis test with Bonferroni correction. To check the prognostic ability of the ACE scores to distinguish individuals with cerebellar lesions from controls, as well as from those with cerebral lesions, receiver operating characteristic (ROC) analysis was utilized by assessing the area under the ROC curve area under curve (AUC). All statistical analyses were performed using SPSS.

Table 1. The comparison in ACE III test scores between patients with cerebellar lesions and patients with supratentorial lesions and controls

Screening test	Cerebellar lesion patients	Supratentorial lesion patients	Controls	χ^2	Eta^2	*p* overall	Post hoc (Dunn-Bonferroni test)		
							Cerebellar/ Controls	Supratentorial/ Controls	Cerebellar/ Supratentorial
ACE III total	83.00[a] (75.00[b]; 91.00[c])	76.50 (64.50; 86.00)	94.00 (86.00; 98.00)	37.78	0.25	**.000**	**0.002**[d]	**0.000**	0.123
ACE attention	16.00 (16.00; 17.00)	16.00 (13.00; 17.00)	17.00 (17.00; 18.00)	15.42	0.08	**.000**	**0.043**	**0.000**	1.000
ACE memory	20.00 (15.00; 24.00)	17.00 (12.00; 21.00)	23.00 (20.00; 25.00)	24.23	0.15	**.000**	0.156	**0.000**	**0.031**
ACE fluency	9.00 (5.00; 10.00)	8.00 (5.00; 10.00)	12.00 (9.00; 14.00)	19.17	0.11	**.000**	**0.001**	**0.000**	1.000
ACE language	25.00 (22.00; 26.00)	24.00 (20.00; 25.00)	26.00 (26.00; 26.00)	29.67	0.18	**.000**	**0.002**	**0.000**	0.107
ACE visuospatial functions	15.00 (11.00; 16.00)	14.00 (9.50; 16.00)	16.00 (16.00; 16.00)	28.94	0.21	**.000**	**0.004**	**0.000**	0.417
ACE memory retrieval	4.00 (2.00; 6.00)	3.00 (1.00; 5.00)	6.00 (5.00; 7.00)	25.42	0.16	**.000**	**0.014**	**0.000**	0.372
ACE memory recognition	5.00 (4.00; 5.00)	4.00 (3.00; 5.00)	5.00 (4.00; 5.00)	11.28	0.05	**.003**	1.000	**0.017**	0.142
ACE fluency perseveration	0.00 (0.00; 1.00)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	2.60	0.01	.272	1.000	1.000	0.803
ACE fluency intrusions	0.00 (0.00; 1.00)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	10.83	0.05	**.004**	**0.056**	1.000	0.179

Note: Results were corrected for multiple comparisons (Bonferroni corrections). ACE = Addenbrooke's cognitive examination. [a]Median, [b]lower quartile, [c]upper quartile, and [d]significance.

Results

The Comparison in the ACE III Scores Between Patients with Cerebellar Lesions, Patients with Supratentorial Brain Lesions and Controls

To show the differences in cognitive functioning between patients with cerebellar lesions, patients with supratentorial brain lesions, and individuals without brain damage (controls), we performed the Kruskal-Wallis Test and post hoc comparisons (with Bonferroni correction) between these three groups. The results are shown in Table 1.

The results indicated that patients with cerebellar lesions differed from controls in the ACE III total score, as well as in all the ACE III domains scores, except the memory domain, whereas participants with supratentorial brain lesions varied from the control group on the ACE III total score, and all of the ACE III domain scores. Patients with supratentorial brain damage obtained significantly lower scores on the ACE III memory domain than subjects with cerebellar lesions.

Regarding the memory domain, subjects with cerebellar lesions performed worse than controls in terms of retrieval; however, not in terms of recognition, whereas patients with supratentorial lesions obtained significantly worse results than controls in both retrieval and recognition tasks.

Qualitative analysis of fluency domain scores revealed that participants with cerebellar lesions, unlike those with supratentorial damage, made significantly more intrusions than controls. However, the groups with brain damage did not differ from the controls in the number of perseverations.

The Comparison in the ACE III Scores Between Patients with Cerebellar Lesions, Patients with Supratentorial Frontal Lesions, Patients with Supratentorial Non-Frontal Lesions and Controls

We intended to characterize the cerebellar cognitive profile in contrast to supratentorial brain lesion profile. According to functional neuropsychological topography of the brain lobes, we distinguish patients with frontal lobe lesions, connected mostly with metacognitive and executive functioning and patients with temporal, parietal, and occipital lobe lesions, gathered as one group, co called "non-frontal group," functionally linked mostly with perception, sensory, and associative ability.

Table 2. Comparison in ACE III test scores between patients with cerebellar lesions, patients with supratentorial frontal lesions, and patients with supratentorial non-frontal lesions and controls

Screening test	Cerebellar lesion patients	Supratentorial frontal lesion patients	Supratentorial non-frontal lesion patients	Controls	χ^2	Eta^2	*p* overall
ACE III total	83.00[a] (75.00[b]; 91.00[c])	77.00 (57.50; 86.50)	72.50 (66.00; 85.00)	94.00 (86.00; 98.00)	36.80	0.25	**.000**
ACE attention	16.00 (16.00; 17.00)	16.00 (13.00; 17.00)	15.50 (13.00; 17.00)	17.00 (17.00; 18.00)	15.81	0.08	**.001**
ACE memory	20.00 (15.00; 24.00)	17.00 (11.00; 23.00)	15.00 (12.00; 21.00)	23.00 (20.00; 25.00)	24.15	0.15	**.000**
ACE fluency	9.00 (5.00; 10.00)	8.00 (5.50; 9.50)	8.00 (5.00; 11.00)	12.00 (9.00; 14.00)	19.60	0.11	**.000**
ACE language	25.00 (22.00; 26.00)	22.00 (19.50; 25.00)	24.00 (20.00; 25.00)	26.00 (26.00; 26.00)	31.91	0.21	**.000**
ACE visuospatial functions	15.00 (11.00; 16.00)	14.00 (10.00; 16.00)	14.00 (9.00; 16.00)	16.00 (16.00; 16.00)	29.51	0.19	**.000**
ACE memory retrieval	4.00 (2.00; 6.00)	2.50 (1.00; 5.50)	3.00 (0.00; 5.00)	6.00 (5.00; 7.00)	28.34	0.18	**.000**
ACE memory recognition	5.00 (4.00; 5.00)	5.00 (3.00; 5.00)	4.00 (3.00; 5.00)	5.00 (4.00; 5.00)	13.64	0.06	**.003**
ACE fluency perseveration	0.00 (0.00; 1.00)	0.00 (0.00; 1.00)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	10.21	0.04	**.016**
ACE fluency intrusions	0.00 (0.00; 1.00)	0.00 (0.00; 1.00)	0.00 (0.00; 0.00)	0.00 (0.00; 0.00)	26.53	0.16	**.000**

Note: ACE = Addenbrooke's cognitive examination. [a]Median, [b]lower quartile, and [c]upper quartile.

Table 3. Post hoc comparison in ACE III test scores between patients with cerebellar lesions, patients with supratentorial frontal lesions, and patients with supratentorial non-frontal lesions and controls

Screening test	Post hoc comparisons (Dunn-Bonferroni test)					
	Cerebellar lesion/Controls	Frontal lesions/Controls	Non-frontal lesions/Controls	Cerebellar lesions /Frontal lesions	Cerebellar lesions/Non-frontal lesions	Frontal lesions/Non-frontal lesions
ACE III total	**0.004**[a]	**0.000**	**0.000**	0.993	0.279	1.000
ACE attention	0.078	**0.022**	**0.001**	1.000	1.000	1.000
ACE memory	0.321	**0.004**	**0.000**	0.880	**0.030**	1.000
ACE fluency	**0.003**	**0.000**	**0.004**	1.000	1.000	1.000
ACE language	0.062	**0.000**	**0.000**	0.097	0.491	1.000
ACE visuospatial functions	**0.007**	**0.000**	**0.000**	0.423	1.000	1.000
ACE memory retrieval	**0.025**	**0.001**	**0.000**	1.000	0.284	1.000
ACE memory recognition	1.000	0.581	**0.012**	1.000	0.104	1.000
ACE fluency perseveration	1.000	1.000	1.000	1.000	0.450	0.348
ACE fluency intrusions	0.113	0.090	1.000	1.000	**0.025**	**0.019**

Note: ; Results were corrected for multiple comparisons (Bonferroni corrections). ACE = Addenbrooke's cognitive examination. [a]Significance.

To examine the differences in the ACE III scores between patients with cerebellar lesions, patients with supratentorial frontal lesions, and patients with supratentorial non-frontal, lesions, and controls, we performed the Kruskal-Wallis Test and Dunn's post hoc tests (with Bonferroni correction) between these four groups. The results are shown in Tables 2 and 3.

The results indicated that patients with cerebellar lesions performed worse than controls in the ACE III total score, ACE III attention, ACE III fluency, and ACE III visuospatial functions. Both frontal and non-frontal supratentorial lesion groups obtained significantly lower results in the ACE III total score, as well as on all of the ACE III cognitive domains when compared with controls. The analyses also revealed a significant difference between the cerebellar lesion group and the non-frontal supratentorial lesion group in the ACE III memory domain: the non-frontal lesion group obtained significantly lower results. In terms of the memory domain, all three groups of patients with brain damage performed worse than controls in retrieval tasks; however, regarding recognition, only the non-frontal supratentorial lesion group scored lower than controls. In the fluency domain, subjects

Table 4. Comparison in ACE III test scores between patients with cerebellar lesions, patients with supratentorial frontal lesions, and patients with supratentorial temporal lesions and controls (Kruskal-Wallis)

Screening test	Supratentorial temporal lesion patients	χ^2	Eta^2	*p* overall
ACE III total	78.00[a] (72.00[b]; 88.00[c])	27.84	0.25	**.000**
ACE attention	16.00 (13.00; 17.00)	12.22	0.09	**.007**
ACE memory	17.00 (12.00; 21.00)	16.15	0.13	**.001**
ACE fluency	10.00 (6.00; 12.00)	19.11	0.16	**.001**
ACE language	24 00 (18.00; 25.00)	27.96	0.25	**.001**
ACE visuospatial functions	15.00 (13.00; 16.00)	25.07	0.22	**.001**
ACE memory retrieval	3.00 (1.00; 5.00)	19.44	0.17	**.001**
ACE memory recognition	4.00 (3.00; 5.00)	8.50	0.06	**.037**
ACE fluency perseveration	0.00 (0.00; 0.00)	6.24	0.03	.101
ACE fluency intrusions	0.00 (0.00; 0.00)	16.71	0.14	**.001**

Note: Median and upper and lower quartile for patients with cerebellar lesions and patients with supratentorial frontal lesions and controls were reported in Table 2. ACE = Addenbrooke's cognitive examination. [a]Median, [b]lower quartile, and [c]upper quartile.

Table 5. Post hoc comparison in ACE III test scores between patients with cerebellar lesions, patients with supratentorial frontal lesions, and patients with supratentorial temporal lesions and controls

Screening test	Post hoc comparisons (Dunn-Bonferroni test)					
	Cerebellar lesion/Controls	Frontal lesions/Controls	Temporal lesions/Controls	Cerebellar lesions/Frontal lesions	Cerebellar lesions/Temporal lesions	Frontal lesions/Temporal lesions
ACE III total	**0.004**[a]	**0.000**	**0.001**	0.993	1.000	1.000
ACE attention	0.078	**0.022**	0.082	1.000	1.000	1.000
ACE memory	0.321	**0.004**	**0.005**	0.880	0.503	1.000
ACE fluency	**0.003**	**0.000**	0.600	1.000	1.000	0.635
ACE language	0.062	**0.000**	**0.006**	0.097	1.000	1.000
ACE visuospatial functions	**0.007**	**0.000**	**0.016**	0.423	1.000	1.000
ACE memory retrieval	**0.025**	**0.001**	**0.003**	1.000	1.000	1.000
ACE memory recognition	1.000	0.581	**0.047**	1.000	0.229	1.000
ACE fluency intrusions	0.113	0.090	1.000	1.000	0.052	**0.039**

Note: Results were corrected for multiple comparisons (Bonferroni corrections); ACE fluency perseveration subscale was omitted because the results of the Kruskal-Wallis test were not significant. ACE = Addenbrooke's cognitive examination. [a]Significance.

with cerebellar lesions and patients with frontal supratentorial damage made significantly more intrusions than the non-frontal supratentorial lesion group.

In order to make this non-frontal supratentorial group more homogeneous, we additionally decided to differentiate participants with only temporal lobe lesions as a separate group, as it could be argued that, given the prominent roles of both parietal and frontal lobes in attention (Li et al., 2017), the parietal lesion patients (included in the non-frontal group) could perform similarly to frontal group in some tasks. The exclusion of patients with occipital lesion was based on their very low numbers in the non-frontal supratentorial lesion group. Choosing the temporal lesion group as functionally contrasting to the frontal lesion group was based on the different cognitive functions of this brain region, connected mainly with memory, perception, and sensory experience. The results are shown in Tables 4 and 5.

Selecting a group of temporal lesion patients did not radically change the previous findings. However, compared with previous results obtained from the heterogeneous non-frontal group, the temporal lesion group did not obtain lower results in the ACE III attention and fluency domains than controls. Significant difference in the memory domain observed previously between more heterogeneous non-frontal group, and cerebellar lesion group did not occur between the temporal lesion group and the cerebellar lesion group.

To check if visual problems or presence of hydrocephalus significantly affected obtained results, we performed statistical calculations excluding the patients with visual impairment and then with hydrocephalus from the cerebellar lesion group. The exclusion of patients with visual disturbances did not change the previous results in any way. The results of statistical analyses after the exclusion of patients with hydrocephalus were also the same except for only one difference in post hoc comparisons: after this exclusion, the difference between cerebellar lesion patients and non-frontal supratentorial lesion patients in ACE III memory subdomain disappeared ($p = .149$).

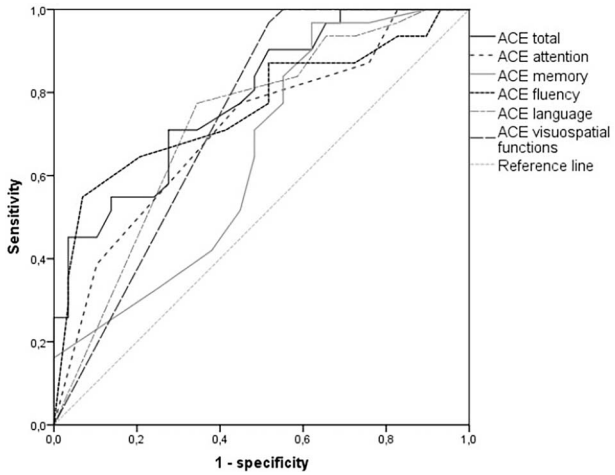

Fig. 1. The ROC curves for individual cognitive functions and the ACE III total score (cerebellar lesion group vs. controls). ROC = receiver operating characteristic; ACE = Addenbrooke's cognitive examination.

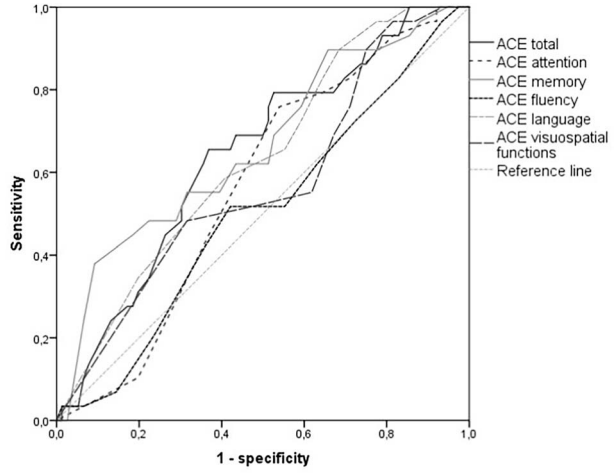

Fig. 2. The ROC curves for individual cognitive functions and ACE total score (supratentorial lesion group vs. cerebellar lesion group). ROC = receiver operating characteristic; ACE = Addenbrooke's cognitive examination.

The information about lesions size was collected only in the group of cerebellar lesion patients. The tumors in this group varied between 2295 and 47,025 mm^3 ($M = 13{,}256.929$, $SD = 15{,}532.35$). Spearman's correlation analysis showed no significant associations between the size of the tumor and scores obtained by these patients in the ACE III scales (all p values $> .05$).

As vermis damage may affect motor functions significantly and cognitive functions indirectly, we checked the results once again, this time excluding vermis lesions participants from the analyses. It turned out that descriptive statistics, as well as all of the effect sizes and significance levels in multigroup comparisons, were very similar (almost identical). Therefore, after thorough, consideration we decided to keep these cases in the dataset.

The Prognostic Ability of the ACE III to Distinguish Individuals with Cerebellar Lesions from Controls and from Patients with Supratentorial Brain Lesions—ROC Analysis

To check the prognostic ability of the ACE III scores to distinguish individuals with cerebellar lesions from those without brain damage, as well as from those with supratentorial brain lesions, the ROC analysis was utilized (see Fig. 1 and Fig.2) by assessing the area under the ROC curve (AUC). Statistically significant AUC values were obtained for the ACE III total score, as well as subscales measuring fluency, visuospatial functions, language, and attention—meaning that these factors differentiates patients with cerebellar lesions from healthy controls. All of these values were above 0.7. When the ability of the ACE III to differentiate patients with cerebellar lesions from patients with supratentorial brain lesions was assessed, significant AUC values were obtained only for the ACE III total score, as well as for the subscales measuring memory and language (Table 6).

Table 6. Descriptive statistics for AUC based on the ROC curves

Variables	AUC	Standard Error	*p*	95% CI for AUC	
				Lower	Upper
Cerebellar lesion group versus controls					
ACE total	0.785	0.057	**.000**	0.673	0.898
ACE attention	0.712	0.067	**.005**	0.582	0.843
ACE memory	0.646	0.072	.053	0.504	0.788
ACE fluency	0.760	0.063	**.001**	0.637	0.884
ACE language	0.724	0.067	**.003**	0.593	0.854
ACE visuospatial functions	0.732	0.067	**.002**	0.601	0.864
Supratentorial lesion group versus cerebellar lesion group					
ACE_total	0.644	0.058	**.023**	0.530	0.758
ACE_attention	0.567	0.058	.289	0.454	0.680
ACE_memory	0.662	0.061	**.011**	0.543	0.780
ACE_fluency	0.502	0.062	.971	0.380	0.624
ACE_language	0.632	0.058	**.038**	0.518	0.745
ACE_visuospatial_functions	0.569	0.063	.276	0.446	0.692

Note: AUC = area under the curve; ROC = receiver operating characteristic; CI = confidence interval; AUC < 0.5 = the variable does not differentiate patients; 0.5 ≤ AUC < 0.6 = the variable very poorly differentiates patients; 0.6 ≤ AUC < 0.7 = the variable differentiates patients adequately; 0.7 ≤ AUC < 0.8 = the variable differentiates patients satisfactorily; 0.8 ≤ AUC < 0.9 = the variable differentiates patients very well; 0.9 ≤ AUC = the variable differentiates patients perfectly.

Table 7. Suggested cut-off points based on the Youden index

Cognitive function	Cut-off point	Sensitivity	Specificity	ACC	PPV	NPV
Cerebellar lesion group versus controls						
ACE total	89[a]	0.71	0.72	0.72	0.73	0.70
ACE attention	17	0.77	0.55	0.67	0.65	0.70
ACE fluency	12	0.55	0.93	0.73	0.90	0.66
ACE language	26	0.77	0.67	0.71	0.69	0.73
ACE visuospatial functions	15	0.97	0.48	0.73	0.67	0.93
Supratentorial lesion group versus cerebellar lesion group						
ACE total	81[b]	0.66	0.63	0.64	0.40	0.83
ACE memory	24	0.38	0.91	0.76	0.61	0.79
ACE language	21	0.90	0.32	0.48	0.34	0.89

Note: ACC = accuracy measure; PPV = positive predictive value; NPV = negative predictive value; ACE = Addenbrooke's cognitive examination.
[a]Score equal or higher indicates lack of lesions.
[b]Score equal or higher indicates cerebral lesion.

Optimal cut-off points for each subscale with significant AUC, as well as for the ACE III total score, were determined using the highest Youden index calculated as follows: (Sensitivity + Specificity) − 1. Cut-off points are presented in Table 7 along with sensitivity, specificity, and accuracy measures.

Discussion

The results obtained in the present study proved that the ACE III presents good sensitivity and diagnostic specificity in the assessment of cognitive dysfunctions of patients with cerebellar lesions. The ROC analysis showed high prognostic ability of the ACE III scores to distinguish individuals with cerebellar lesions from controls, with 71% sensitivity, 72% specificity, and 72% accuracy for the 89 cut-off point. Patients with cerebellar lesions obtained lower results not only in the ACE III total score, but also in every cognitive domain except for memory. It suggests that word fluency, visuospatial functions, language, and attention domain may successfully differentiate patients with cerebellar lesions from individuals without brain damage. Optimal cut-off points were determined for these cognitive domains. The sensitivity for the cut-off values ranged from 55% (for the fluency domain) to 97% (for the visuospatial domain). The specificity ranged from 48% (for the visuospatial domain) to 93% (fluency domain) and accuracy from 0.67 (attention domain) to 0.73 (fluency and visuospatial domain).

The results also indicated that the ACE III can be applied to differentiate cerebellar lesion patients from supratentorial brain lesion patients. In the current study, individuals with cortical lesions obtained significantly lower results than cerebellar patients in the ACE III total score, with the cut-off score of 81, it was characterized by satisfactory sensitivity of 66%, specificity of

63%, and accuracy of 64%. In comparison to cerebellar patients, those with supratentorial brain damage presented significantly lower results only in the two ACE III domains: memory and language, with cut-off points of 24 and 21 points, respectively. It was characterized by 38% and 90% sensitivity and 91% and 32% specificity.

In light of the clinical observation that cerebellar damage tends to result in mild cognitive impairment, much more subtle than that observed in cortical lesions, the question appeared whether the cognitive screening tool could be sensitive enough to detect slight neuropsychological dysfunctions associated with cerebellar lesions. Our results showed that the ACE III meets these requirements. Although other screening tests, such as the MoCA and the MMSE are available in Polish, the specificity of the MMSE for mild cognitive dysfunctions is characterized by a ceiling effect (Pendlebury, Mariz, Bull, Mehta, & Rothwell, 2012). Moreover, none of those methods offer such extended scoring, rating up to 100 points and the possibility of describing such a detailed cognitive profile of the patient. The ACE III scores correlate with the standard diagnostic neuropsychological tests results, used in the assessment of attention, language, verbal memory, and visuospatial function, taking into account the level of sensitivity and specificity (Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013). Moreover, the ACE III is considered the most sensitive tool for assessing daily functioning of a patient (Giebel & Challis, 2017). Its previous version (the ACE-R) has successfully been administered in clinical practice as an extension of cognitive assessment when the results provided by shorter diagnostic methods were inconclusive (Velayudhan, Ryu, & Raczek, 2014). Our results indicated that the ACE III can be used to evaluate cognitive functioning in patients with other than dementia group of impairments. This finding is consistent with the previous observation of the ACE III utility in estimating the intellectual functioning of SM patients (Figlus et al., 2018), stroke patients (Lees et al., 2017), and patients after surgery for brain tumors (Cherkil et al., 2017; Kerrigan et al., 2011; Tymowski et al., 2018).

The findings of our study are in line with the idea of the so-called "Schmahmann's syndrome" or CCAS which, in its cognitive part, encompasses impairments of executive functions (abstract thinking, WM, and problem-solving), visuospatial abilities (spatial organization and mental rotation) and language (aphasia, apraxia, and dyslexia) in individuals with cerebellar lesions (Schmahmann, 2010). The ACE appeared to be applicable for all mentioned areas and the results of the current study confirmed that cerebellar patients had problems in the attention, language, fluency, visuospatial, and executive domains.

The presence of sporadic visual disturbances in the group of cerebellar lesion patients, such as diplopia or nystagmus, as well as the presence of hydrocephalus, did not change the obtained results.

Previous studies also emphasize the role of cerebellar damage in some aspects of attention. For instance, Gottwald et al. (2003) showed that patients with focal cerebellar lesions demonstrated distinct deficits in qualitative aspects of divided attention tasks, accompanied with unimpaired selective attention. In turn, Haarmeier and Their (2007), in their review paper questioned the ideas of "attentional cerebellum", as well as "dysmetria of attention" and claimed that a closer look at the paradigms used in several studies reporting attention deficits in patients with cerebellar damage, reveals disturbances only in tasks involving significant oculomotor, motor, and/or WM demands. Interestingly, in our research, the cerebellar group differed significantly in the results of the ACE III Attention subdomain only in relation to the control group. We expected better results in terms of attention in the cerebellar patients compared with the supratentorial lesion group, because cognitive disorders in the case of injuries of the cerebellum are described as rather moderate and usually not as visible as in case of cerebral patients. However, in our study, patients with cerebellar lesions displayed problems in the serial subtraction task, which is considered to be an example of WM examination, which suggests their WM impairments. The lower ability in serial subtraction possibly caused the decrease in the results for the whole Attention ACE III domain. The role of the cerebellum in regulating the WM function has already been described in many previous studies concerning both verbal WM (Kirschen et al., 2009; Riva & Giorgi, 2000; Shortman et al., 2014) and visuospatial WM (Starowicz-Filip, Chrobak, Kwiatkowski, Milczarek, & Rajtar-Zembaty, 2019).

Our findings showed the association between cerebellar lesions and the decrease of visuospatial processes which is consistent with results obtained by other authors. Some prior studies provide strong support for the hypothesis that lesions of cerebellar circuits affect spatial tasks, such as mental rotation of objects (Starowicz-Filip, 2017; Tedesco et al., 2011), line bisection judgment (Fink, Marshall, & Shah, 2005), spatial orientation (Lee et al., 2005), spatial attention (Hildebrandt, Spang, & Ebke, 2002), spatial WM (Ronnberg, Rudner, & Ingvar, 2004), spatial learning (Petrosini, Leggio, & Molinari, 1998) or even navigation through virtual environment (Moffat, Elkins, & Resnick, 2006). Interestingly, patients with cerebellar lesions primarily reveal problems with tasks relying on mental manipulation of objects, which require spatial imagination ability, however, not with constructive tasks, where direct manipulation of objects is possible (Molinari et al., 2004). Such problems were also reported in children with cerebellar damage who underwent low-grade astrocytoma surgery (Starowicz-Filip, Chrobak, Milczarek, & Kwiatkowski, 2017).

In the current study, patients with cerebellar lesions obtained lower scores in the language ACE III domain, which involves naming objects, repeating words and sentences, writing, and reading. Previous research also confirmed that individuals with cerebellar damage not only presented articulatory impairments connected with dysarthria, but also manifested language problems. In some cases, cerebellar lesions caused grammatical problems in speech and flexion, as well as difficulties in detecting

syntactic errors during speech (Justus, 2004; Moretti & Brava, 2002). The presence of cerebellar aphasia still rises controversies, but there are some studies, which confirm aphasic problems of patients with right-sided cerebellar lesions, accompanied with retained ability to name objects, slightly impaired spontaneous speech, programming of elaborate utterances and their initiation (Barczak, Marcinowicz, & Kochanowski, 2011; Blancart, Escrig, & Gimeno, 2011; De Smet, Engelborghs, Paquier, De Deyn, & Mariën, 2011; Mariën et al., 1996). This deficit pattern was analogous to that observed in transcortical motor aphasia. Cerebellar mutism syndrome is an extreme example of a cerebellar language problem (Pollack, 1997). Lower ACE III fluency scores obtained in our study are in line with previous research, based on MRI and TMS examination, which showed a negative impact of cerebellar damage on fluency (phonological fluency in particular) (Arasanz et al., 2012; Hubrich-Ungureanu, Kaemmerer, Henn, & Baus, 2002).

The cerebellar patients and the control group did not differ significantly in the ACE III memory scores, what is more, cerebellar patients performed significantly better in this domain than patients with cortical damage. It is also worth noting that in our study patients with cerebellar damage displayed problems with retrieving information from long-term memory, but not in recognizing it. The same difference between recalling words from long-term memory storage and their recognition was observed in children after cerebellar astrocytoma surgery (Starowicz-Filip et al., 2019). Those children needed external clues to access remembered information, without this help they had problems with recalling it at the precise time. These results suggest that the process of encoding and storage of learned information may be intact in the cerebellar lesion group in contrast to retrieval difficulties. Learning difficulty, problems with spontaneously recalling new information, deficient encoding strategies, and difficulty locating information in memory stores were also described in adults with cerebellar lesions (Koziol et al., 2014). Moreover, some studies confirm the regulating role of the cerebellum in Ph-STM (Timmann & Daum, 2007) and episodic memory (Andreasen et al., 1999).

The role of the cerebellum in cognitive processes is also supported by neuroanatomy and neuroimaging data. Although the cerebellum has connections with almost every part of human brain, from the cognitive perspective the existence of pathways between the cerebellum and prefrontal cortex, as well as between the cerebellum and posterior parietal cortex, seemed to be especially important (Grimaldi & Manto, 2011; Ramnani, 2006). The cognitive profile comparison between cerebellar lesion and supratentorial lesion patients demonstrated that the "cerebellar" cognitive profile appears somewhat more similar to that observed with frontal lobe damage. The results showed that, in case of the memory domain both the cerebellar and the frontal lesion group revealed decreased ability to retrieve previously learned material compared with controls, whereas the non-frontal lesion group (contained patients with temporal, parietal, and occipital lobe lesions) presented lower results in memory trace storage. This group obtained lower results than controls not only in retrieval tasks, but also in recognition of previously learned material.

The frontal-like profile of the cerebellar patient can be described with the dissociation between recall and recognition of previously learned material (with better recognition), distinctive for frontal lesions (Turner, Cipolotti, Yousry & Shallice, 2007), as well as with more pronounced dysexecutive syndrome, with lower scores of mental shifting, flexibility and lower scores of inhibition (more intrusions in the fluency test). The similarity of the observed cerebellar memory impairment profile to frontal memory deficits could be explained by the anatomical and functional connections between these two brain structures: the fronto-ponto-cerebellar tracts and the cerebello-thalamo-frontal tracts (Schmahmann, 1998). Similarly, the frontal-like memory profile connected with cerebellar lesions was also observed in pediatric patients with low-grade cerebellar astrocytoma (Starowicz-Filip et al., 2019). Those children manifested partial memory deficits with WM impairments, dissociation between recall and recognition of previously learned material (with better recognition), high susceptibility to proactive interference, and problems with learning process organization.

In our study, the analysis of the fluency domain scores indicated that patients with cerebellar lesions and patients with frontal supratentorial lesions made significantly more intrusion errors than the non-frontal supratentorial lesion group. Moreover, when we separated the non-frontal group and listed only the temporal lesion group of patients, the latter group did not differ significantly in terms of verbal fluency and attention from the control group, unlike in the case of cerebellar and frontal groups of patients where differences in fluency and attention with the control group were significant. This result may additionally confirm the similarity between the cerebellar lesion patients' profile and the frontal lesion profile in contrast to the temporal lesion profile (Aita et al., 2019).

Our study has some limitations that warrant mention. The most important one is the overly heterogeneous group of cerebellar lesion patients, which included not only patients with tumors of the cerebellum, but also patients after a stroke of this brain structure or with vascular malformations. Moreover, patients with cerebellar tumors also differed significantly in terms of histology and WHO grade classification. Similarly, the group of patients with supratentorial brain tumors was also too heterogeneous. As research shows (Gempt et al., 2017), a higher degree of brain tumor malignancy, according to the WHO classification, is one of the risk factors for weaker cognitive functioning of the operated patient. When planning further research on this topic, we should ensure a better and more homogeneous selection of cerebellar lesion patients to the study

group. Moreover, the tumor or lesion size should be included not only in the cerebellar lesion group of patients but also in the supratentorial lesion group of patients. Additionally, we did not use any questionnaires assessing the emotional functioning of the patients, which may have significantly affected their cognitive performance. Some of our patients presented slight problems with emotions, being more depressed, irritable, impulsive, with less criticism of behavior, but we made this observation only during the clinical psychological interview. Future research should include an assessment of the emotional state based on a standardized questionnaire.

Conclusions

1. The ACE III (Hodges & Larner, 2017) appeared to be a useful screening tool for assessing the cognitive functioning of patients with cerebellar damage.
2. The ACE III test shows high diagnostic accuracy, good sensitivity, and specificity in the assessment of cognitive dysfunctions in patients with focal cerebellar lesions.
3. Our study determined the cut-off point in the ACE III total score, and the ACE III cognitive domains for individuals with cerebellar lesions, in comparison to subjects without organic brain damage.
4. The ACE III cognitive profile of patients with cerebellar lesions is in line with cerebellar CCAS, with problems in the attention, language, fluency, visuospatial, and executive domains.
5. The cerebellar cognitive profile, in comparison to the results of supratentorial brain lesion patients, is similar to that observed in patients with frontal lobe damage with decreased ability to retrieve previously learned material, impaired word fluency, and executive dysfunctions.
6. The ACE III has great potential and usefulness for clinical practice, especially that there is a lack of a single cognitive instrument verified in the group of patients with cerebellar damage. Cerebellar lesion patients are often neglected in terms of neuropsychological evaluation; meanwhile, the ACE III can be used as a short screening tool in the clinics of neurology, neurosurgery, or neurological rehabilitation to quickly assess their cognitive performance. Short time of ACE III implementation along with its high sensitivity is particularly positive in the case of neurosurgical patients who usually require rapid pre-operative neuropsychological diagnosis. The profile of cognitive dysfunctions in individual domains obtained in the examination may constitute a useful basis for further planning of patients' neuropsychological rehabilitation.

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