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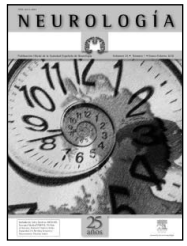

ORIGINAL ARTICLE

Cognitive event-related brain potentials (P300) in patients with normal pressure hydrocephalus. Results of a prospective study

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KEYWORDS
Normal pressure hydrocephalus;
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Abstract
Objective: To determine the response to cognitive event-related potentials (P300) in patients with normal-pressure hydrocephalus (NPH) and their relationship with clinical and cognitive status before and after shunt surgery.
Methods: We performed a prospective study in a series of 26 patients with NPH who underwent clinical and cognitive assessment before surgery and 6 months afterwards. Visual P300 potentials obtained before and after treatment were also compared with those obtained in 18 healthy volunteers.
Results: Before shunting, the P300 wave was detected in 11 (42.3%) NPH patients, compared with the 18 (100%) volunteers. Six months after shunting, the P300 wave was found in 20 (76.9%) NPH patients. P300 latency was significantly longer in NPH patients than in the control group before surgery, but not at 6 months after surgery. No significant differences in neuropsychological studies or in the level of dependence for daily life activities were found between the subgroups of NPH patients with and without pre-surgical P300 waves, or between changes in P300 parameters and clinical and cognitive changes.
Conclusions: The P300 wave was delayed or undetectable in a substantial percentage of patients with NPH before surgery. These alterations can be reversed by shunting. P300 analysis and neuropsychological tests could be complementary measures to evaluate functional status in patients with NPH.

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PALABRAS CLAVE
Hidrocefalia de presión normal;
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Potenciales evocados cognitivos;
Potenciales evocados visuales;
P300

Potenciales evocados cognitivos (P300) en pacientes con hidrocefalia de presión normal

Resumen
Objetivos: Determinar la respuesta a los potenciales evocados visuales (P300) en pacientes con hidrocefalia de presión normal (NPH) antes y después de la implantación de una derivación de líquido cefalorraquídeo (LCR) y establecer su relación con la situación clínica y cognitiva antes y después del tratamiento quirúrgico.
Métodos: Estudio prospectivo en una serie de 26 pacientes con NPH a los que se realizó una valoración clínica y neuropsicológica y se analizó la P300 antes y 6 meses después del tratamiento quirúrgico. Los resultados de la P300 de los pacientes antes y después del tratamiento se compararon con los de un grupo control de 18 voluntarios sanos.
Resultados: Once de los pacientes con una NPH (42,3%) presentaron onda P300 antes del tratamiento quirúrgico, mientras que esta onda estaba presente en los 18 individuos del grupo control (100%). La latencia de la onda fue significativamente superior en los pacientes que en el grupo control. Seis meses después de la implantación de la derivación de LCR, 20 (76,9%) de los pacientes con NPH presentaron la onda P300, sin que hubiera diferencias significativas en las latencias de la onda entre ambos grupos. No hubo diferencias en los estudios neuropsicológicos y en el grado de independencia en la realización de las actividades de la vida diaria entre los pacientes que presentaron la P300 antes de la cirugía y los que no la presentaron, ni entre los cambios de la P300 y los cambios clínicos o cognitivos después del tratamiento quirúrgico.
Conclusiones: Un porcentaje importante de pacientes con una NPH no presentan onda P300 o su latencia está incrementada. Estas alteraciones pueden revertirse en muchos pacientes al implantar una derivación de LCR

Introduction

Normal-pressure hydrocephalus (NPH) is a syndrome in which patients present abnormal gait, urinary incontinence and cognitive disorders in the context of a dilated ventricular system. The clinical case may completely or partially improve after implanting a cerebrospinal fluid (CSF) shunt[1]. This entity is one of the few treatable causes of dementia. However, despite the increasing prevalence of this syndrome and the publication of clinical practice guidelines, there is still controversy about the diagnosis and treatment of these patients. In patients with suspected syndrome, studies of CSF dynamics and continuous monitoring of intracranial pressure constitute the main pillars of NPH diagnosis. A neuropsychological assessment helps to establish a differential diagnosis with other causes of cognitive impairment and to quantify the patient's baseline condition at diagnosis, as well as to assess the changes after surgery.

Several authors have suggested that the P300 wave generated upon applying visual or auditory stimuli (event-related potentials [ERP]) can be a useful tool for objectively assessing some cognitive functions such as attention and short-term memory[2-4]. The P300 wave is a positive voltage deflection with latency of 300 ms in the EEG. P300 analysis (presence of the wave, latency and amplitude) helps to determine the prior cognitive state and the changes that occur after treatment[5,6]. Relationships have been established in patients with Alzheimer's disease, Parkinson's disease, multiple sclerosis and post-traumatic syndrome between P300 onset latency and the patient's level of cognitive functioning[7-17]. These patients may have an increase in the generation latency of the P300 that is associated with a deterioration of cognitive abilities. After treatment, when patients improve, the wave latency is often reduced.

To date, there is only one study (published in 1993) that analysed the P300 in patients with NPH[18]. That study registered auditory cognitive potentials and carried out a simultaneous neuropsychological evaluation on a group of 7 patients with NPH before and after surgical treatment. The authors concluded that there was an association between postoperative improvement of cognitive status and reduced latency and increased amplitude of the P300 waveforms.

The objectives of this study were: *a*) to determine the characteristics of the P300 wave in a series of patients diagnosed with NPH and compare them with those of a control group, *b*) to identify the changes that occur in P300 latency and amplitude after surgical treatment, and *c*) to establish the relation between P300 amplitude and latency and the cognitive state of patients before and after implanting a CSF shunt.

Patients and methods

Prospective study of a series of 37 patients diagnosed with NPH admitted consecutively at the Neurosurgery Department of Vall d'Hebron University Hospital between March 1995

and April 1998. All patients had a history of gait disturbance, cognitive impairment and/or sphincter incontinence associated with a dilated ventricular system (Evans index > 0.3)[19]. According to the study protocol in our service[20-22], the presence of an alteration in CSF dynamics (resistance to CSF reabsorption > 10 mmHg/ml/min) or the presence of B waves in a percentage ? 10% of the graphic registry of the intracranial pressure (ICP)[21] was confirmed in all cases and a ventriculo-peritoneal (VP) CSF shunt with a low opening pressure was implanted. From the initial series of 37 patients, 8 were discarded because they had no visual potentials or they were very pathological, thus invalidating the result of cognitive potentials; 3 patients were discarded due to inadequate monitoring. The final series included 26 patients (13 males and 13 females, with an average age of 70.9 ± 8.6 [49-82] years). All 26 underwent clinical and neuropsychological assessment and had cognitive and visual evoked potentials recorded before surgery and 6 months after surgical treatment.

The results of the neuropsychological examination and the P300 (latency and amplitude) were compared with a control group of 18 healthy volunteers with no neurological or neuropsychological background (9 males and 9 females, with an average age of 68.8 ± 5.7 [62-81] years) recruited among hospital staff or relatives and acquaintances of patients. No significant differences were found between the ages of the patient group and the control group ($U = 175.5$; $p = 0.258$). Both patients and volunteers agreed to participate in the study after being informed and made aware of its characteristics and objectives. A written consent was obtained for the invasive examinations necessary for the diagnosis of the disease in patients. However, given the non-invasive nature of the P300, verbal consent was considered sufficient for it. The information generated by all the studies carried out on the patients and volunteers involved in the study was treated in accordance with the principles of Law 15/1999 on Data Protection.

Clinical and neuropsychological evaluation

The NPH scale designed at our centre[23] was used to establish the degree of clinical condition of the patients. This determines the severity of the syndrome through its three main symptoms: gait disturbance, cognitive impairment and sphincter incontinence. The minimum score possible is 3 points: the patient is bedridden, has no contact with the environment and suffers urinary and faecal incontinence (vegetative state or minimally conscious). A maximum score of 15 corresponds to a normal gait, no objective or subjective changes in sphincter control and lacking cognitive impairment or demonstrated only through comprehensive neuropsychological assessment (Table 1).

In addition to the NPH scale, functional scales designed to assess the degree of independence in performing activities of daily living were applied to each patient or next of kin: Rapid Disability Rating Scale-2 (RDRS-2), which assesses the degree of dysfunction in activities of daily living (ADL) on 18 items rated from 1 (no need for assistance to carry out activities) to 4 (inability to carry out the task)[24], and the Informant Questionnaire, which records subjective cognitive changes observed by a close relative from the response to 17 items rated from 1 (best) to 5 (worst)[25,26].

Table 1 Scale of normal-pressure hydrocephalus

Assessment of gait (M)	
Bedridden patient. Lacking independent ambulation	1
Walking autonomously but with help	2
Walking autonomously but with help	3
Abnormal but stable gait	4
Normal gait	5
Cognitive functions (CF)	
Patient in vegetative state or minimally conscious	1
Severe dementia	2
Memory disturbances with behavioural disorders	3
Alteration of recent memory	4
Cognitive disorders objectified only by specific tests	5
Sphincter control (SC)	
Urinary and faecal incontinence	1
Continuous urinary incontinence	2
Occasional urinary incontinenc	3
Micturition urgency	4
Normal sphincter control	5

The score of the patient is derived from the sum of the scores in the three sections: M + CF + SC.

The neuropsychological assessment included several tests designed to assess various cognitive aspects, such as memory, speed of information processing and frontal lobe functions[22,27]. The tests selected were as follows: Trail Making Test (TMT) A and B, which assess psychomotor speed, divided attention and mental flexibility; verbal fluency, where patients have to name as many animals as possible in 1 min; and the Digits Forward and Backward from the Wechsler Memory Scale, which quantifies attention and working memory.

Neurophysiologic evaluation

The P300 wave was evoked visually using a methodology called "oddball" with a BrainLAB device. During the test, binocular visual stimuli were presented in a reversible draughts board on a 19" TFT monitor at full screen resolution with a luminance of 90 cd/m^2; the target stimulus was presented on the monitor on a red and black board and a distracting stimulus was presented on a black and white board. The size of the board tiles used was 30' of visual arc. Each test consisted of 82 distracting stimuli and 18 target stimuli. The stimuli were applied randomly, one every 2 s. Patients were instructed to count the number of target stimuli mentally; at the end of each trial, they were asked the total number of stimuli detected. The same examiner always scored both evoked and cognitive potentials of patients and controls. In order to confirm the reproducibility of the measurements, there were two trials on each individual. If the number provided by the subject tested was wrong, both tests were repeated.

The average evoked potentials were computed separately at Fz, Cz and Pz for each trial and stimulus category (target/non-target), through a semiautomatic peak detection program (BrainLAB). In this study, the P300, which is usually identified as the broadest positive wave at the Pz level that appears within 300 to 600 ms after presentation of stimulus[28] (Fig. 1), was rated between 300 and 750 ms, as it was considered that the latency could be prolonged[29].

To rule out possible visual disturbances that could interfere with the test results, it was verified that all patients and healthy volunteers had normal visual evoked potentials, evaluated separately in each eye. To reduce possible artefacts, visual and cognitive evoked potentials were recorded under the same conditions, for both patients and the healthy volunteers, and always between 15:00 and 16:00. To avoid the influence of postprandial sleepiness, patients and volunteers had finished lunch before 13:00.

Statistical analysis

The statistical analysis was performed using the SPSS package, version 12.0 (SPSS Inc., Chicago, Illinois, USA). The Kolmogorov-Smirnov test was used to set the rate of distribution of variables. The variables that followed a normal distribution were described through the average and standard deviation, and those that followed a non-normal distribution, using the interquartile range. In the statistical analysis, the following nonparametric tests were used: *a*) comparison between groups: Mann-Whitney U test; *b*) comparison of preoperative and postoperative variables: the Wilcoxon rank test; *c*) analysis of differences in the frequency in each case: Fisher and McNemar tests (χ^2); and *d*) correlation between variables: the Spearman rank correlation test. Furthermore, we calculated the percentage of preoperative and postoperative neuropsychological changes using the formula:

(after surgery – before surgery) / before surgery x 100

Differences were considered statistically significant when the value of $p < 0.05$.

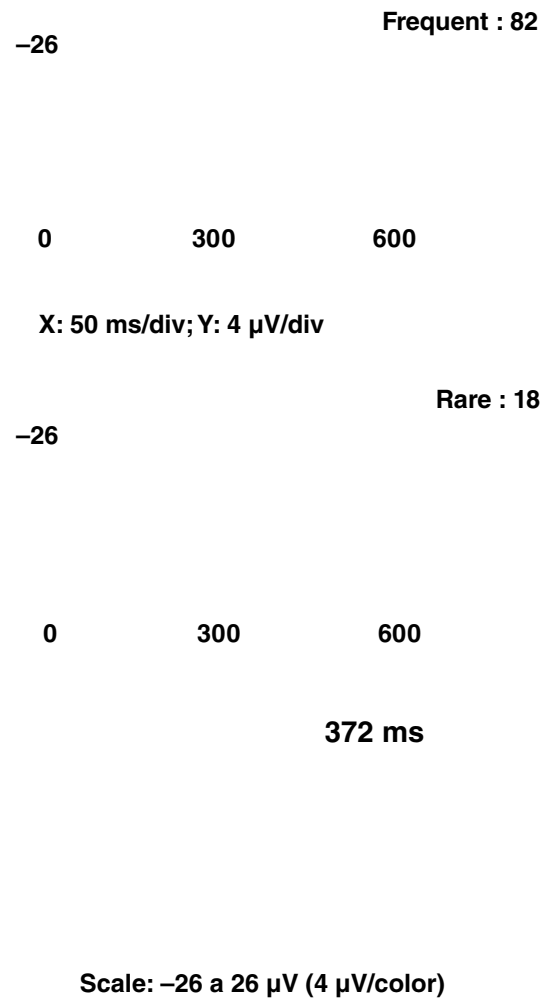

Figure 1 P300 wave obtained in one of the control group volunteers. The P300 appears at 372 ms (arrow) and shows an amplitude of 19.2 µV. The three lines of the graphs that appear in different shades of grey correspond to the response recorded in the electrodes placed on the interhemispheric fissure at the level of the frontoparietal fissure Fz, vertex Cz and the parietooccipital Pz fissure.

Results

Clinical symptoms

Before surgery, 19 patients (73%) presented the complete clinical triad, 5 patients (19%) presented abnormal gait or sphincter incontinence with cognitive disorders and 2 patients (7.6%) presented cognitive impairment alone. Six months after the implantation of a VP CSF shunt, 23 patients (88%) showed clinical improvement (increase of 1 or more points on the NPH scale). According to this scale, gait improved in 20 patients (83%), cognitive function in 13 patients (50%), and sphincter incontinence in 17 patients (85%). The clinical changes detected after surgery were statistically significant, both in assessing the total NPH scale score ($U = -4.21$; $p < 0.001$) and its three individual components: gait ($U = -4$; $p < 0.001$), incontinence ($U = -3.29$; $p = 0.001$) and cognitive function ($U = -3.12$; $p = 0.002$).

Presence of P300

Prior to implanting the CSF shunt, the P300 wave was identified in only 11 of the 26 patients with NPH (42.3%). In contrast, this wave was observed in all 18 subjects tested (100%) in the control group. These differences were statistically significant ($p < 0.001$). Six months after surgery, 20 (76.9%) of the patients with NPH presented the P300 wave (the 11 patients who showed responses before treatment continued having them after the intervention), and these differences were statistically significant when compared to the figures before surgery ($p = 0.035$). After implanting the CSF shunt, the differences between the group of patients with NPH and the control group disappeared ($p = 0.125$).

Table 2 P300 Parameters in the patients and in the control group

P300	Patients (n = 8/ 26)		Controls (n =18/ 18)
	Before	After	
Latency	420 (49,5)	414 (73,5)	396 (39)
Pz amplitude	14.6 (7,35)	18.2 (10,04)	11 (9.11)

Pz: electrode located at the confluence of the interhemispheric fissure with the parietooccipital fissure.
Statistically-significant differences in preoperative latency values between patients and controls and postoperative amplitude values between patients and controls.

Characteristics of P300

Considering the 8 patients who presented the P300 before and after surgery, the median latency of the preoperative P300 wave was 420 [interquartile range, 49.5] ms and the median of the amplitude, 14.6 [7.345] μV. At 6 months after implanting the CSF shunt, the median of the P300 wave latency was 414 [73.5] ms and the amplitude, 18.2 [10.04] μV (Table 2). Wave latency was not reached in any of the patients treated. Figure 2 shows the example of the P300 in a patient with NPH recorded before and 6 months after surgical treatment.

In the control group, the median P300 latency was 396 [38] ms and the amplitude, 11 [9.11] μV. The comparative analysis between the P300 wave components in the control group and the group of patients with NPH before and after surgical treatment showed an increased P300 wave latency ($U = 30.5$; $p = 0.027$) in patients before surgery, but not 6 months after implanting the CSF shunt ($U = 36.5$; $p = 0.066$). The wave amplitude was similar in both groups before surgery ($U = 35$; $p = 0.057$). However, 6 months after surgical treatment, the patients showed a higher amplitude than the control group ($U = 34$; $p = 0.049$) (Table 2).

Functional and neuropsychological evaluation

A comparative analysis between the neuropsychological and functional assessments of the 26 patients before and after surgical treatment showed significant differences in the TMT B ($U = -1.956$; $p = 0.05$) and in the functional scales: RDRS-2 ($U = -3.09$; $p = 0.002$) and in the Informant Questionnaire ($U = -3.66$; $p < 0.001$) (Table 3). Although most patients showed improvement in the results of other neuropsychological tests applied, the changes were not significant when the results of the series of patients were evaluated as a group.

Relations between the neuropsychological evaluation and the P300 components

Prior to implanting a CSF shunt, 11 patients presented the P300 wave and 15 did not. No significant differences were found in age, years of schooling or duration of symptoms among those patients who showed the P300 wave and those who did not. No significant differences in the neuropsychological assessment or the functional scales in both patient subgroups were found either. After surgical treatment, no significant correlations were found between changes in the P300 parameters and the percentage of change in the clinical or neuropsychological parameters.

Discussion

This study objectifies the features of the P300 obtained by analysing the cognitive evoked potentials obtained in a series of 26 patients with confirmed diagnosis of NPH, as well as the changes induced by surgery in the wave appearance and components. It also evaluates the relationship of the P300 wave with the clinical and neuropsychological characteristics of the patients before and after implanting a CSF shunt. Our results indicate that the P300 wave was observed in a significantly higher proportion of control subjects than in patients with NPH before surgical treatment. The wave could not be identified in 15 (57.7%) patients with NPH and, in the group in which it could be identified, the latency was always greater. Six months after surgery, P300 was detected in 20 (76.9%) of the patients studied. There was no difference in the control evaluation between patients and the control group. Neither was there a difference in the percentage of attainment of the P300 or in its latency.

It is known that the presence of the P300 reflects discrimination or attention to the presentation of stimuli, so this wave is not obtained in patients with attention problems[30]. Studies of evoked potentials with long latency carried out in patients with non-neurological disorders, but which involve cognitive deficits and impaired attention and vigilance, as in the case of obstructive sleep apnoea syndrome (OSAS), support the hypothesis that attention deficit is crucial in the cognitive impairment observed in OSA[17]. This deficit, specific to attention processes, is associated with an alteration in frontal cortical activity[31]. Frontal functions, which involve cortical and subcortical structures, are especially affected in NPH; this could explain the differences observed between the control group and the group of patients with NPH before implanting a CSF shunt.

Our results are consistent with those of the study by Quadrale et al.[18]. These authors objectified that, in 2 of 7 patients (28.6%) with NPH studied, it was not possible to observe P300 presence before or after surgery, while the remaining 5 patients showed higher preoperative latency times, with a decrease in latency after surgery. Although

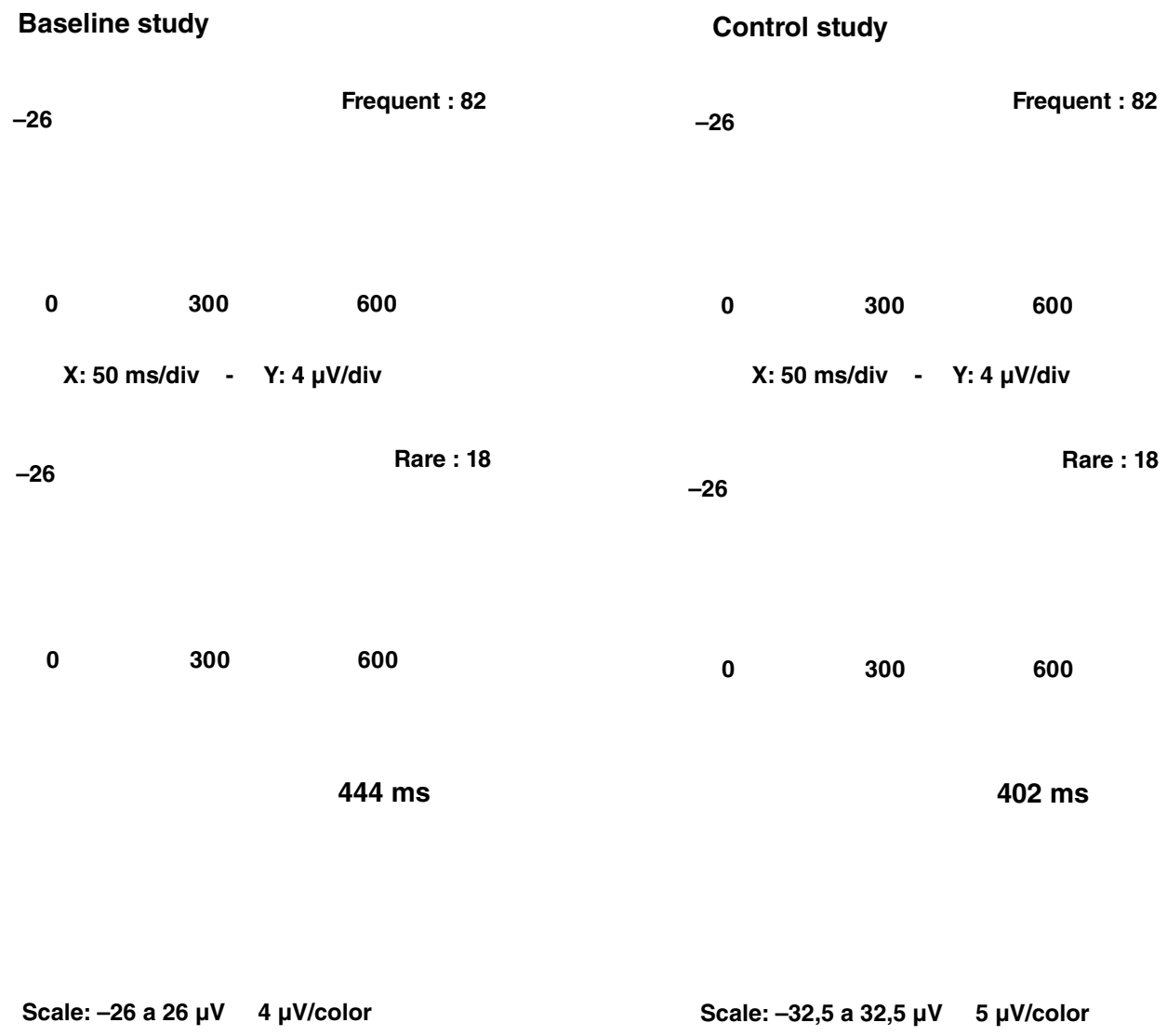

Figure 2 Visual-cognitive evoked potentials in a 74-year-old patient with normal-pressure hydrocephalus before surgery and 6 months after the placement of a ventriculo-peritoneal cerebrospinal fluid shunt. The preoperative score of the patient in the NPH scale was 10 (gait: 3; higher functions: 4; sphincters: 3); 6 months after surgery, it was 13 (gait: 5; higher functions: 4; sphincters: 4). Note that P300 wave latency was reduced after surgical treatment (B), going from a latency of 444 to 402 ms (arrows). After surgery, P300 amplitude (Pz) increased from 16.9 to 22.9 µV. The three lines of the graphs that appear in different shades of grey correspond to the response recorded in the electrodes placed on the interhemispheric fissure at the level of the frontoparietal fissure Fz, vertex Cz and the parietooccipital fissure Pz.

Quadrale et al. found lower preoperative amplitudes in patients with NPH than in the control group, such differences were not statistically significant in our study, which may be due to different sample sizes. Paradoxically, we observed that, after surgery, P300 amplitude in patients was higher than in the control group volunteers.

Some studies indicate that P300 amplitude is proportional to attention requirements for a given task[32]; a reduction in P300 amplitude can therefore be attributed to a reduction in attention. One possible explanation for the results obtained in the current study would be that patients with NPH require further activation of neural circuits to complete a given task[33-35].

Before implanting a CSF shunt, patients with NPH presented the characteristic clinical triad of this syndrome along with a low score in the functional scales and the neuropsychological studies carried out. The objectified neuropsychological results could be due to impairment of the attentional processes and of the executive or prefrontal functions. Six months after surgery, gait improved in 83% of patients, incontinence in 85% and cognitive status in 50% of patients. In addition, patients showed improved attention and mental flexibility (TMT B) along with greater independence for activities of daily living (RDRS-2) and, according to the assessment carried out by their families, an increased functional capacity (Informant Questionnaire).

Table 3 Scores of the neuropsychologic assessment and clinical tests

	Before	After	p
Neuropsychologic tests			
Forward digit	5 [2]	5 [2]	0.247
Backward digits	3 [3]	3 [1]	0.289
TMT A	90 [112,5]	121 [115]	0.881
TMT B	219 [135]	166 [155]	0.05
Verbal fluency	11 [5,75]	12 [4.75]	0.083
Functional scales			
Escala NPH	10 [5]	13 [3]	< 0.001
NPH gait	3 [2]	4,5 [1]	< 0.001
NPH cognition	4 [1]	4 [1]	0.002
NPH incontinence	3 [2,25]	5 [1]	0.001
RDRS-2	30 [14,75]	25 [6.25]	0.002
Informant questionnaire	56 [14]	37 [16.75]	0.006

NPH: normal-pressure hydrocephalus; (RDRS-2: Rapid Disability Rating Scale-2; TMT: Trail Making Test.
The data expresses the median [interquartile range].

However, in contrast to the study by Quadrale et al.[18], P300 presence, latency and amplitude were not associated with clinical or cognitive changes. Although the patients who did not present the P300 performed more poorly in cognitive tests and functional scales, we found no statistically-significant differences with patients who did present this wave. No significant correlations between P300 changes and postoperative cognitive improvement were found either. We must consider that our study is observational and our sample size may be insufficient to show these differences.

One might attribute the differences observed between this study and the results of Quadrale et al. to methodological differences or to different sample sizes (26 vs. 7 patients), and those authors also used different neuropsychological tests[18]. In addition, in the study by these authors, a potential learning effect (test-retest) cannot be excluded, as patients were evaluated six times after surgery, with an interval of less than 1 month between doses. Another aspect to consider is the impact of external factors in assessing ERP response. Polich et al.[36] objectified the influence of factors such as temperature or time of day in the responses to ERP performed at different times. Although we have tried to control these factors, we cannot ignore this possibility.

Among the limitations of our study, we should also mention the sample size, because, despite being the most extensive series in the literature, the number of patients remains low.

In conclusion, the results of our study indicate that, although implanting a CSF shunt in patients with NPH reduces P300 wave abnormalities, this effect is not associated with the clinical or cognitive changes observed. Studies with a larger sample size are needed to clarify their sensitivity, specificity and predictive value. As long as these studies are not conducted, our findings indicate that the P300 is useful for determining cognitive impairment in patients with NPH, but does not replace conventional neuropsychological assessment. Therefore, the P300 and neuropsychological assessment should be considered complementary in assessing the functional status of patients with NPH, and especially in clinical research studies on this syndrome.

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Conflict of interests

The authors declare no conflict of interests.

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