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Research article

Applicability of auditory event-related potentials to monitor the cerebrospinal fluid tap test

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Abstract: *Objectives:* To investigate whether patients with a positive tap-test (TT) result for iNPH exhibit improved auditory event-related potential (ERP) responses following lumbar puncture. *Design:* Alongside gait and neuropsychological assessment, auditory ERPs were recorded using the oddball paradigm before and after lumbar puncture, with subsequent comparison of responses between the groups. *Study sample:* Forty elderly individuals suspected of iNPH were enrolled, with 20 showing a negative TT result and 20 with a positive TT result. *Results:* Participants with a positive TT result demonstrated a significant decrease in P2 latency in the left ear, of approximately 5.15 ms, and a tendency toward statistical significance for P3 latency in the right ear, of approximately 27.65 ms, after lumbar puncture, compared to those with a negative TT result. However, an increase in amplitude was not observed in subjects with a positive TT result. *Conclusions:* The reduction of the P2 and P3 latencies following lumbar puncture was associated with a positive TT result. Thus, latency analysis of these components holds promise in supporting TT results in individuals suspected of iNPH. Therefore, auditory ERP results could be useful as an auxiliary tool alongside the TT in the investigation of iNPH.

Keywords: hydrocephalus, normal pressure; evoked potentials, auditory; event-related potentials, P300; cerebrospinal fluid shunts; neurophysiology

Abbreviations: Normal pressure hydrocephalus (NPH); Cerebrospinal fluid (CSF); Idiopathic NPH (iNPH); Tap test (TT); Event-related potentials (ERP)

1. Introduction

Normal pressure hydrocephalus (NPH) was initially described in 1965 as a syndrome characterized by a triad of symptoms: gait disturbance, urinary incontinence, and cognitive dysfunction. It results from abnormal cerebrospinal fluid (CSF) accumulation leading to ventricular enlargement, while intracranial pressure remains within normal limits [1]. Predominantly affecting individuals aged 60 years and older, NPH may be classified as idiopathic (iNPH), when symptoms occur without an identifiable cause, or secondary, when associated with acquired neurological conditions such as meningitis, traumatic brain injury, or subarachnoid hemorrhage [2]. Despite decades of research, the diagnosis of iNPH remains challenging, and accurate identification of patients who are likely to benefit from shunt surgery is still a major clinical issue [3–7].

Because auditory event-related potentials (ERP) provide objective and non-invasive measures of cortical auditory and cognitive processing, they may help improve diagnostic assessment in iNPH. Therefore, the alternative hypothesis of the present study was that patients with a positive CSF tap-test (TT) response would demonstrate improved auditory ERP responses after lumbar puncture, characterized by reduced latencies and/or increased amplitudes. The null hypothesis was that no significant ERP changes would occur, and that auditory ERP would not contribute to TT-related diagnostic assessment.

Treatment of iNPH consists of CSF diversion through shunt surgery, most commonly ventriculo-peritoneal, ventriculo-atrial, or lumbo-peritoneal shunts [6–8]. To temporarily simulate shunt effects and estimate surgical prognosis, the CSF TT is commonly used. This procedure involves gait and neuropsychological assessment before and after lumbar puncture with removal of 30–50 mL of CSF, and clinical improvement after the procedure suggests a greater likelihood of postoperative benefit [9,10]. Although the TT is widely used, additional complementary tools may improve diagnostic accuracy and prognostic assessment [5,7,8,11,12].

The auditory ERP records voltage changes generated in thalamocortical regions expressed as positive (P) and negative (N) waves [13]. Initial processing stages give rise to the P1 and N1 components, reflecting the integrity of the auditory pathway, neural coding, and the perception and detection of the acoustic stimulus. Subsequently, the emergence of P2 and N2 components is associated with the classification and decoding of the acoustic stimulus [14,15]. The later processing stages yield the P3 component, directly linked to the cognitive function integrity [13–15], providing insights into auditory abilities such as attention, discrimination, and temporal processing [14–16].

Each component can be analyzed in terms of latency, representing the time taken for it to emerge following stimulus onset (measured in milliseconds), and the amplitude of the peak, quantifying the strength of the response (in microvolts) [17]. Consequently, this method serves as a valuable tool primarily for monitoring alterations in the processing of auditory skills and cognitive functions post-

intervention [18]. Some studies have reported ERP changes after shunt placement in patients with iNPH, suggesting potential utility for neurophysiological follow-up [19–22]. However, no previous studies have investigated auditory ERP responses during the CSF TT. Thus, this study aimed to investigate whether patients exhibiting a positive response of the CSF TT for iNPH would demonstrate enhanced auditory ERP responses following lumbar puncture.

2. Materials and methods

2.1. Study design

A randomized clinical study was conducted involving 40 elderly individuals with suspected iNPH who attended the specific laboratory for the CSF TT between February and September 2023. The research received approval from the institutional Research Projects Appraisal Ethics Committee under number 5.964.351, and all procedures were conducted following ethical guidelines outlined in the World Medical Association Declaration of Helsinki. Before participation, written informed consent was obtained from all participants.

2.2. Sample characterization

All subjects included in the study exhibited neurologic signs and symptoms consistent with iNPH, such as gait disturbance, urinary incontinence, and/or cognitive impairment. Additionally, ventricular enlargement was confirmed through brain imaging data, and CSF opening pressures were between 70 and 245 mm H_2O for all participants.

None of the individuals exhibited obstruction in the external acoustic meatus or conductive impairments. This was confirmed by the presence of a type-A tympanogram [23] pattern for all subjects, indicating normal middle ear function, with no conductive or mixed hearing loss. Furthermore, none of the participants presented with severe or profound sensorineural hearing loss [24].

2.3. Procedures

The CSF TT protocol entailed conducting neuropsychological and gait assessments both before and 2 h after lumbar puncture, during which 30–40 mL of CSF was removed. A positive response of the CSF TT was determined by improved performance in at least one of the assessments [25,26].

The neuropsychological assessment was conducted by a well-trained neuropsychologist in a private and quiet room, with an approximate duration of 30 min. The protocol included the Semantic Verbal Fluency (Animals) test, the Wechsler Adult Intelligence Scale-III (WAIS-III)—Coding and Symbol Search subtests, and the Color Trails Test. Determining a positive response in neuropsychological tests relies on the application of the Reliable Change Index (RCI), a statistical measure employed to evaluate whether a change in an individual's score holds statistical significance (e.g., before and after a particular intervention) [27].

The gait assessment consists of analyzing the patient's walking pattern over a distance of 10 m. A positive response is considered if there is either a 20% reduction in the time taken to complete the route, a 20% decrease in the number of steps, or a 10% improvement in both parameters, provided there is no deterioration in other spatio-temporal parameters [28,29].

In addition to the neuropsychological and gait assessments, auditory ERP testing was carried out both before and 2 h after the lumbar puncture. The testing utilized the two-channel Duet equipment, manufactured by Intelligent Hearing System (Miami, Florida), along with ER 3A insert earphones. The evaluation lasted approximately 30 min, during which the participant remained in a relaxed seated position in a recliner armchair.

Preceding electrode placement, the skin surface (including the forehead, mastoids, and scalp) was cleaned with abrasive paste. Subsequently, Ag-AgCl electrodes were affixed using electrolytic paste and micropore tape. The active electrode was positioned at Cz, while the reference electrodes were placed in M1 and M2 (left and right mastoids), and the ground electrode was situated on the forehead, adhering to the international 10-10 system (International Electrode System). Measures were taken to ensure that electrode impedance remained below 5 kOhms.

The tone-burst stimulus, featuring a Blackman envelope, was monaurally presented within an oddball paradigm. The stimulus was present at a level of 80 dBnHL, with the standard stimulus comprising 85% of the trials at 1000 Hz, and the target stimulus accounting for 15% of the trials at 2000 Hz. A total of 300 sweeps were presented at a rate of 1.1 sweeps per second, with the high- and low-pass filters between 1 and 30 Hz. The response analysis window was set between −100 ms pre-stimulus and 512 ms post-stimulus.

Participants were instructed to attentively focus on the target stimulus and raise one hand whenever the target stimulus appeared. The P1, N1, P2, and N2 components were identified in the standard trial, and the P3 component was identified in the target trial. Absolute latency and peak-to-peak amplitude analyses were conducted for the P1, N1, P2, N2, and P3 components.

2.4. Analyses

A Student's t-test and Fisher's exact test were used to compare the groups according to the positive and negative responses of the CSF TT, across various parameters, including age, presence of gait disturbance, urinary incontinence, cognitive impairment, and presence of mild or moderate hearing loss.

Afterward, the difference in the ERP response for each component, both in terms of latency and amplitude, was calculated by comparing the post-puncture results with the baseline (i.e., ERP response before puncture). This involved subtracting the pre-puncture results from the post-puncture results. Then, a one-tailed independent samples t-test was conducted to verify whether patients with a positive response of the CSF TT exhibited a significant decrease in latency or a significant increase in amplitude compared to patients with a negative response of the CSF TT. The Welch correction was applied when the assumptions of equality of variance between the groups were not satisfied.

For all inferential analyses, a p-value ≤ 0.05 was considered statistically significant.

3. Results

3.1. Study population

Among the 40 elderly people included in the study, 20 exhibited a negative response to the CSF TT, while 20 had a positive response. There were no significant differences observed between subjects

with a positive or negative response of the CSF TT concerning age, presence of gait disturbance, urinary incontinence, cognitive impairment, or presence of mild or moderate hearing loss (Table 1).

Table 1. Characterization of the sample according to CSF TT results.

	Minimum	Maximum	Mean	Standard deviation	Student's t-test
Age (years)					
Positive	62.0	86.0	75.4	6.3	$t = 0.543$
Negative	65.0	84.0	76.4	6.0	$p = 0.590$
		Number of cases with symptoms present		Percentage (%)	Fisher's exact test
Gait disturbance					
Positive		18		90.0%	>0.999
Negative		19		95.0%	
Urinary incontinence					
Positive		12		60.0%	>0.999
Negative		12		60.0%	
Cognitive impairment					
Positive		14		70.0%	>0.999
Negative		15		75.0%	
Mild or moderate hearing loss					
Positive		17		85%	0.605
Negative		19		95%	

3.2. Auditory ERP

Figure 1 illustrates two waveform examples categorized by CSF TT results.

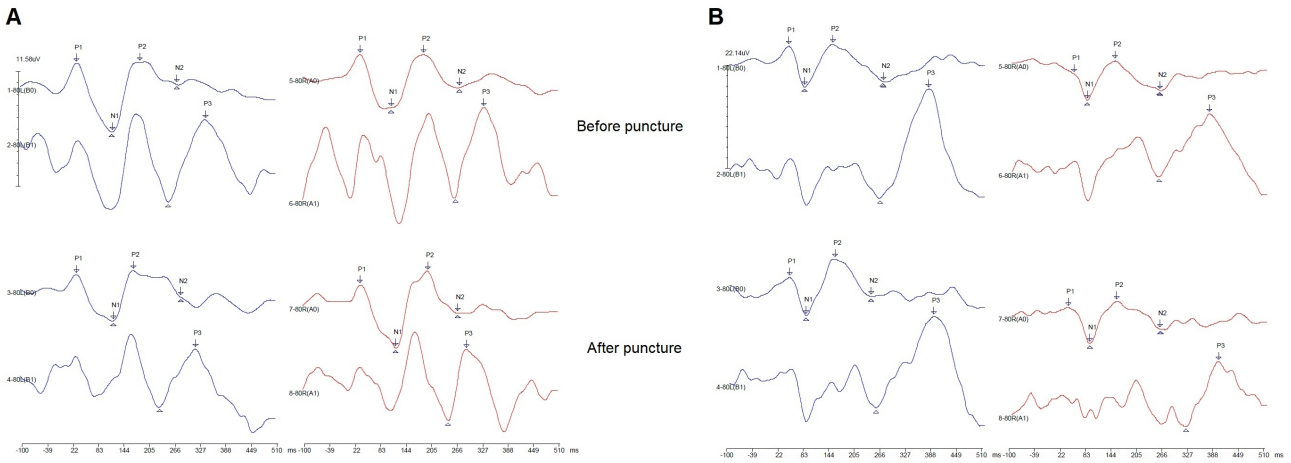

Figure 1. Waveforms examples from a subject with a positive response of the CSF TT (A) and a subject with a negative response of the CSF TT (B).

Elderly individuals with a positive response to the CSF TT presented a significant decrease in the latency of the P2 component in the left ear and a tendency to a statistically significant difference in the latency of the P3 component in the right ear, compared with elderly individuals with a negative response to the CSF TT. The statistical power of the study in both instances was 95%. However, no significant differences were observed in terms of amplitude (see Table 2 and Figure 2).

Table 2. Comparison of the difference in auditory ERP latencies and amplitudes according to the CSF TT result.

	Ear	T-test	Degree freedom	p-value	Cohen's d
P1	Right	−1.824	38.000	0.962	−0.577
	Left	1.126	38.000	0.134	0.356
N1	Right	−0.120	38.000	0.548	−0.038
	Left	0.206	38.000	0.419	0.065
P2	Right	−1.456	38.000	0.923	−0.460
	Left	2.259	38.000	0.015*	0.714
N2	Right	0.447	38.000	0.329	0.141
	Left	−0.245	38.000	0.596	−0.077
P3	Right	1.657	38.000	0.054#	0.524
	Left	1.167	38.000	0.125	0.369
P1-N1	Right	3.420	38.000	0.999	1.081
	Left	0.359	38.000	0.639	0.114
P2-N2	Right	1.769	38.000	0.958	0.559
	Left	−0.221	38.000	0.413	−0.070
N2-P3	Right	0.905	38.000	0.815	0.286
	Left	0.895	38.000	0.812	0.319

Note: * p-value statistically significant; # p-value tending to statistical significant difference.

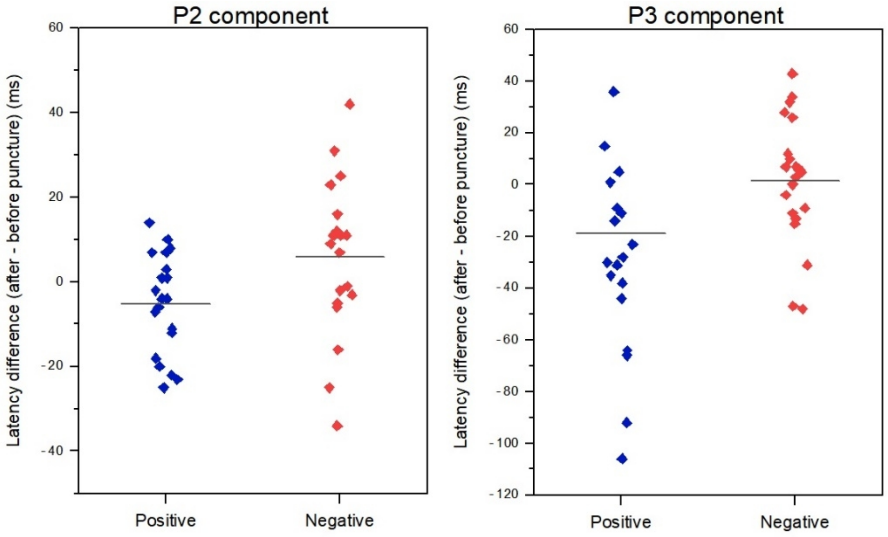

Figure 2. Latency difference of P2 in the left ear and P3 in the right ear, compared between CSF TT results in milliseconds.

4. Conclusions

In light of the imperative to establish standardized methods to bolster CSF TT outcomes, this study sought to explore whether auditory ERP responses could serve as promising tools for measuring clinical improvement during CSF TT.

Auditory ERPs have been employed to track neurophysiological changes across diverse populations following interventions [18]. A decrease in latency and/or an increase in the amplitude of auditory ERP components signify enhancements in information processing, with particular emphasis on the quantitative and clinically relevant measures of the P3 component [18]. Consequently, there is a growing interest in exploring their applicability in aiding the diagnosis of patients with suspected iNPH.

This study found that individuals with a positive predictive value of the CSF TT exhibited a significant reduction in the latency of the P2 component in the left ear following lumbar puncture, in contrast to those with a negative predictive value of the CSF TT. Specifically, patients with a positive predictive value demonstrated an average decrease of 5.15 ms in the latency of the P2 component, while those with a negative result showed an average increase of 5.85 ms in the latency of this component post-lumbar puncture.

A similar trend was observed for the latency of the P3 component in the right ear, although it did not reach the level of statistical significance set for this study. In this instance, individuals with a positive predictive value of the CSF TT presented an average decrease of 27.65 ms in P3 latency, whereas those with a negative result demonstrated no reduction in latency in the right ear and an average increase of 14.89 ms in P3 latency in the left ear.

The auditory ERP response is influenced by various factors, including the number of activated neurons, the extent of neuronal activation, and the synchrony of neural responses. The electrical current generated at the synapse between the inner hair cells of the cochlea and the auditory nerve is propagated through the central auditory pathways. This bioelectrical activity is then transmitted through the CFS, the skull, and the skin, ultimately being detectable by electrodes placed on the scalp [30]. The latency of each ERP component primarily reflects the processing speed of the stimulus.

The generating sites of the P2 component are primarily the temporal lobe and the limbic system [13,31], indicating its involvement in the classification and decoding of auditory stimuli [14,15]. The precise locus of generation for the P3 component eludes clear definition, with suggested areas spanning from the hippocampus to the prefrontal and centro-parietal cortices [13,14,32]. Additionally, the latency and amplitude of the P3 component are subject to alterations according to the attentional and cognitive demands inherent to the listening task [33]. The P3 component is widely considered a cognitive component, reflecting the attentional response to stimuli, and is closely related to the integrity of cognitive functions [13–15]. It offers insights into auditory abilities such as attention, auditory discrimination, and temporal processing [15,16,23].

Regarding the pathophysiology of iNPH, observable abnormalities include physical damage to axons and myelin layers resulting from compression and stretching of the white matter. Additionally, a reduction in gray matter density is commonly noted, particularly in regions such as the thalamus, insula, and caudate nucleus. Besides structural changes, metabolic alterations, neuroinflammation, astrogliosis, and compromised integrity of the blood–brain barrier are believed to contribute to the pathophysiology of iNPH. These factors may result in hypoperfusion and hypoxia, which can lead to structural damage in both white and gray matter within the central nervous system [34].

The decompression of ventricles following CSF puncture leads to the restoration of regional and global blood perfusion and increases the pulsatility of penetrating arteries, thereby ameliorating symptoms through decompression. Therefore, given the robust correlation of the P2 and P3 components with regions such as the thalamus, insula, fronto-parietal, and limbic areas [35], the alterations in latencies detected among patients exhibiting a positive predictive value of CSF TT in this study could potentially be linked to alleviation of damage within these areas, likely stemming from decompression of these areas.

Concerning amplitude, no increase in amplitude was observed in patients with a positive predictive value of the CSF TT, as was initially hypothesized. A previous study has also observed that the latency measure seems to be more effective in determining the normality or abnormality of a result for clinical diagnostic purposes [18].

These preliminary results indicate that the analysis of auditory ERP latency may serve as a predictor to assist in the diagnosis of iNPH. Therefore, future studies with larger sample sizes are warranted to validate these findings. If confirmed, efforts should be made to ascertain the latency variability indicative of a positive predictive value of CSF TT. Furthermore, the importance of longitudinal studies that can track patients over an extended period to explore potential delayed improvements is emphasized, especially in patients with a negative predictive result from the CSF TT. Given the TT's low sensitivity, averaging 58% [36], the high rate of false negatives requires long-term monitoring to associate auditory ERP responses with the clinical outcome.

Author' contributions

LAFS: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Visualization; Writing - original draft; Writing - review & editing. LPM & NPS: Investigation; Data curation; Visualization; Writing - review & editing. HCB, HA, FVP, RBD & CASG: Data curation; Investigation; Visualization; Writing - review & editing. SLAM: Conceptualization; Project administration; Supervision; Validation; Visualization; Writing - review & editing. CGM: Conceptualization; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing - review & editing.

This study was conducted at the Department of Physical, Speech-Language-Hearing, and Occupational Therapy of the Medical School at the University of Sao Paulo (FMUSP) and at the Senne Liquor Diagnostics Laboratory.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Data availability statement

The data supporting this study can be found at: http://200.144.255.9:8086/handle/item/711.

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Conflicts of interest

The authors declare no conflict of interest.

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