

Applause sign in Alzheimer's disease: relationships to cognitive profile and severity of illness

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Received: 24 April 2012/Revised: 2 July 2012/Accepted: 4 July 2012/Published online: 20 July 2012
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Abstract The present study aims to investigate the potential clinical utility of applause sign in Alzheimer's disease (AD), exploring whether it is consequent to the severity of cognitive impairment or to specific neuropsychological profiles. According to the current debate, the role of apraxia is also investigated. A total of 105 patients with AD were enrolled and classified on the basis of the severity of the disease: 37 had mild AD, 38 moderate AD, and 30 severe AD. They were compared to 42 normal subjects. The applause sign was detected using the three clap test. All patients underwent a broad neuropsychological examination and 95 AD patients were tested for the presence of apraxia with a detailed praxis battery. Applause sign was present in all AD patient groups, which showed a significant difference with respect to normal controls, but not between each other. No significant difference was reported between apraxic and non-apraxic patients. Applause sign correlated with measures of frontal lobe dysfunction. No correlations were found between the applause sign and other cognitive functions examined.

Keywords Applause sign · Apraxia · Dementia · Alzheimer's disease · Frontal lobe

Introduction

The three clap test, i.e., asking patients to rapidly clap three times after demonstration by the examiner is a quick test that is easy to perform in daily clinical practice [1]. The three clap test is able to reveal the presence of the "applause sign", a tendency to initiate an automatic program of applause when one is asked to initiate a voluntary program of three claps. The applause sign was originally considered to be a specific sign of progressive supranuclear palsy (PSP) [1]. In this work, patients with PSP, Parkinson's disease, and frontotemporal dementia were compared to normal subjects, and it was demonstrated that the applause sign was exclusively present in PSP. In 2008, Wu et al. investigated the presence of the applause sign in different parkinsonian disorders (PSP, Parkinson's disease, multisystem atrophy, corticobasal degeneration) and Huntington's disease [2]. The applause sign was present in all the diseases examined, making plausible the conclusion that this sign is specific for parkinsonian disorders.

Recently, the presence of the applause sign was investigated in two cortical dementias: frontotemporal dementia (FTD) and Alzheimer's disease (AD) and it was proved that the applause sign was present in both diseases [3].

The impetus for the present study arose from a clinical observation that the applause sign is a frequent finding in AD, especially in the severe stage of AD. As such, the present study aims to confirm this clinical finding and subsequently investigate whether the applause sign can be related to a specific cognitive profile or to the severity of disease. To this end, the applause sign was studied in a wide sample of AD patients who were classified on the basis of the severity of cognitive decline they showed. All patients underwent a detailed neuropsychological examination in order to explore whether the main cognitive

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domains and performance were correlated to the three clap test performance.

In addition, the present work is aimed to add information regarding the nature of the applause sign, which is currently under debate. Some authors have found that the applause sign is more frequent in apraxic disorders and have, therefore, concluded for a possible role of apraxia in generating the applause sign [2]. As such, the present prospective study focuses on the presence of apraxia, and a comparison between patients with and without apraxia will clarify the issue whether apraxia plays a role in generating the applause sign.

Materials and methods

There were 147 subjects enrolled in the study where 105 of the patients were affected by Alzheimer's disease and 42 were healthy. All participants gave their written informed consent, and the study was approved by the local ethics committee.

The diagnosis of Alzheimer's disease was performed by two neurologists with experience in cognitive decline (SL and LP), and it was conducted according to international criteria [4].

In the study, 105 patients with Alzheimer's disease were divided into three groups on the basis of disease severity [5] according to their general cognitive status explored by means of the Mini Mental State Examination (MMSE) [6]: 37 patients were classified as "mild AD" (MMSE score range 21–30), 38 were classified as "moderate AD" (MMSE score range 11–20), and 30 as "severe AD" (MMSE score range 0–10).

Forty-two normal controls, matched for demographic characteristics with the AD patients, were included.

The three clap test was applied to detect the presence of the applause sign (Table 1). According to the literature [1, 2] the subjects were asked to "clap three times as quickly as possible after a demonstration by the examiner". In keeping with the literature [1, 2] the subject's performance was considered normal when he/she clapped three times (score = 3), abnormal when the subject clapped more than three times (2 = four times, 1 = five to ten times, 0 = more than ten times).

A detailed neuropsychological examination was available for all patients enrolled and explored general cognitive status (MMSE), short- and long-term memory (Bisyllabic Word Span [7], Corsi Blocks [7], Rey AVLT [8], Rey figure B delayed recall [9]), executive functions and attention (Luria's motor sequences [10], phonological fluency [8], and the Stroop test [10]), visuospatial abilities (VOSP test [11]), language (naming, reading, and word comprehension [12], verbal fluency [8]),

Table 1 TCT performance in AD patients and normal subjects

TCT performance	Mild AD (37)	Moderate AD (38)	Severe AD (30)	NC (42)
Median	3	3	1.5	3
Range	(0–3)	(0–3)	(0–3)	–
Mean	2.16	2.21	1.77	3
Standard deviation	1.14	1.11	1.13	–
<i>N</i> (%) of positive applause sign	14 (37.8)	14 (36.8)	18 (60)	0

TCT three clap test

constructional praxis (the Rey figure B test [9]). A detailed praxis battery [9] was applied to 95 AD patients and, on the basis of their performance, they were classified into 27 apraxic and 68 not-apraxic patients.

Results

The four groups of subjects examined were correctly matched for demographical features as they did not differ significantly in age (mild AD: mean 76.2 ± 6.6 , moderate AD: 78.8 ± 5.9 , severe AD: 78.1 ± 9 , controls: 75.1 ± 7.7 ; ANOVA: all comparisons not significant (ns)), education (mild AD: mean 7.2 ± 3.6 , moderate AD: 5.5 ± 2.7 , severe AD: 4.9 ± 3.7 , controls: 7.2 ± 4.1 ; ANOVA: all comparisons ns) and sex (mild AD (male/female): 13/24, moderate AD: 11/26, severe AD: 9/21, controls: 16/26; χ^2 : all comparisons ns).

The AD groups showed a similar age of onset of the disease (mild AD: mean 74.7 ± 6.7 , moderate AD: 75.9 ± 5.9 , severe AD: 72.7 ± 7.9 ; ANOVA: all comparisons ns) and, as expected, they differed significantly from each other in terms of disease duration (mild AD: mean 1.3 ± 0.6 , moderate AD: 2.8 ± 0.9 , severe AD: 5.9 ± 1.6 ; ANOVA: all comparisons $p < 0.0001$).

Since the three clap test scores are ordinal data, median and range were calculated. For better comparability with previous works [1, 2], mean and standard deviation were also reported.

The percentage of subjects with an abnormal applause sign (number of subjects who obtained a score <3 in the three clap test) was reported.

Table 1 shows that normal controls did not manifest problems in performing the applause sign, and all subjects reached a score of 3. By contrast, an abnormal applause sign was present in all AD patient groups with different frequencies (37.8 % in mild AD, 36.8 % in moderate AD and 60 % in severe AD).

The Kruskal–Wallis test revealed a significant difference between the groups ($\chi^2 = 29,940$, $df = 3$, $p < 0.001$).

The Mann–Whitney test showed that all AD groups differed significantly from healthy subjects: normal controls performed better than mild AD groups ($U = 483,000$, $p < 0.001$), moderate AD groups ($U = 504,000$, $p < 0.001$), and severe AD groups ($U = 252,000$, $p < 0.001$). No significant differences were found between the three AD groups (mild AD vs. moderate AD $U = 691,000$, $p = 0.88$, mild AD vs. severe AD $U = 448,000$, $p = 0.14$; moderate AD vs. severe AD $U = 447,000$, $p = 0.09$), meaning that even if the applause sign was more frequent in the severe AD group, the difference detected between the groups did not reach statistical significance.

The comparison between apraxic (TCT performance: median 3 (0–3); mean 2.16 ± 1.14 ; positive applause sign 33.8 %) and non-apraxic patients (TCT performance: median 3 (0–3); mean 2.29 ± 1.05 ; positive applause sign 36.8 %) failed to show a significant difference in the three clap test performance ($U = 768,500$, $p = 0.16$).

A significant correlation of the applause sign to background neuropsychology was detected in tests exploring executive functions such as Luria's motor sequences (r_s : 0.62, $p = 0.02$), the Stroop test (r_s : -0.58 , $p = 0.019$).

In order to give more reliable support to the cognitive mechanisms of the applause sign than to separate correlations, a multiple regression analysis was performed. Using the stepwise method, a significant model emerged ($F_{1,89} = 5.403$, $p = 0.024$, adjusted R square = 0.68). The Stroop test was a significant predictor variable in this model ($\beta = -0.29$; $p = 0.02$). All the other cognitive variables, including measures of general cognitive decline such as the MMSE test, were not significant predictors in this model.

Discussion

The present prospective study shows that the applause sign is a common finding in patients with Alzheimer's disease (AD). It was present in all AD patient groups examined with a higher frequency in the severe AD group (60 %) compared to the mild and moderate AD groups, which showed a similar percentage (37.8 and 36.8 %, respectively). Even if the applause sign was more frequent in the severe AD group, there was no significant difference between the three AD groups examined, which were classified on the basis of disease severity. The clap sign performance was not predicted by a general cognitive level. The only significant predictor variable was the Stroop test, a test pertinent to executive functions.

The data reinforce the concept that the applause sign is a sign that is not exclusively pertinent to parkinsonian disorders, but it is present in many neurodegenerative diseases. Moreover, the data also support the notion that the applause sign is a frequent finding in AD.

The reason for the higher frequency of this sign in severe AD could be attributable to a more prominent frontal dysfunction that the patients show in this phase of the disease.

In this regard, it is well known from neuropathological data that the degenerative process in Alzheimer's disease starts in the mesial temporal lobes, which later spreads to other cortical areas [13, 14]. The frontal lobe is involved in the degeneration as well, but that generally occurs in the late stages of the disease [13, 14]. Likewise, from a clinical and neuropsychological point of view, AD is characterized by early and prominent episodic memory impairment. In its severe stages, a behavioral and cognitive frontal syndrome is generally evident [15].

On the basis of the above evidence, it is plausible that the higher frequency of the applause sign in severe AD can be reasonably attributed to frontal lobe dysfunction and not merely to disease severity.

The present data contribute to clarify the debated nature of the applause sign. Wu and colleagues [3] suggested apraxia as the possible cause of the applause sign because in their study the clap sign was detected as more frequent in apraxic patients suffering from corticobasal degeneration with respect to other parkinsonian disorders, such as Parkinson's disease, multisystem atrophy, and progressive supranuclear palsy. In our previous work, while exploring the clap sign in cortical dementias [4], the presence of apraxia was an exclusion criterion, and it was demonstrated that patients without apraxia showed the applause sign. However, since apraxic patients were not studied, it did not allow us to exclude a possible role of apraxia as a contributing factor to the generation of the applause sign.

The present work demonstrates that the presence of apraxia does not interfere with the performance in the three clap test, which allows us to rule out the hypothesis that the applause sign is consequent to apraxia. We believe that the applause sign is a motor perseveration, consequent to frontal lobe dysfunction. The fact that favors this hypothesis is that the applause sign exclusively correlates with the performance in tests exploring executive functions.

In this regard, one should expect that the applause sign would have been predicted by the other test exploring motor behavior. Although a correlation was found between the Luria motor sequence test and the applause sign, the multiple regression analysis did not confirm this data. The Luria motor sequence test is traditionally considered a "frontal lobe" motor task. The score of this test corresponds to the number of correct sequences executed, and it is influenced by any kind of motor error such as sequence errors, omissions, and motor perseverations. We speculate that the applause sign exclusively reflects a perseverative behavior and should not necessarily be associated to

performance in other tests exploring motor planning and motor execution.

However, the nature of the applause sign still remains uncertain, and a more detailed exploration of the neuropsychological profile of patients showing the applause sign, such as the potential correlation of the applause sign with other measures of motor perseveration, should clarify the nature of this debated sign.

In conclusion, the present study shows that the applause sign is a frequent finding in patients with Alzheimer's disease, ranging from 30 to 40 % in mild and moderate phases, and up to 60 % in the severe stage. Even if it is a more frequent finding in the severe stage of AD, there is no evidence for considering the applause sign to be an index of disease severity. The higher frequency of the applause sign in the severe stage of AD is likely due to the fact that patients in this stage frequently show a dysexecutive syndrome. Even though the nature of the applause sign is still to be understood, apraxia can be excluded as a factor that causes it. The current study provides further support to the recent findings that challenge the notion of applause sign as a specific sign of parkinsonian disorders and allows us to reformulate the potential clinical role of the applause sign. We suggest that in clinical practice the “three clap test” should be used as a quick test to detect a frontal lobe dysfunction rather than as a test that is able to reveal a “prototypical sign” of specific neurological diseases.

Conflicts of interest The authors have no competing interests.

Ethical standard All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards and laid down in the 1964 Declaration of Helsinki.

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