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ORIGINAL ARTICLE

“Don’t know” sign: description and evaluation of its diagnostic accuracy for cognitive impairment

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Abstract

Objectives Patients in neurology clinics are sometimes not aware of the reason for the consultation, and we have called this circumstance the “Don’t know” sign (DKS). Our objective was to define this new sign and its modalities and to evaluate its prevalence and its diagnostic accuracy for cognitive impairment (CI) in comparison to other observation-based signs.

Design, setting, and participants: A cross-sectional prospective study included all new outpatients evaluated by the authors at neurology consultation.

Measurements We recorded observation-based signs. The Global Deterioration Scale (GDS) was used to assess the cognitive status of patients, based on clinical history, caregiver interview, and cognitive test results. We analyzed the prevalence and the diagnostic accuracy for CI of DKS, “head turning sign,” “attending with,” verbal repetition, and combinations, calculating sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV).

Results We enrolled 673 consecutive patients (62% female) with a mean $\pm$ SD age of 59.3 ± 20.2 years. DKS was positive in 94 patients (14%) and was strongly associated with GDS score. DKS had a Se of 0.41, Sp of 0.98, PPV of 0.89, and NPV of 0.79 for CI diagnosis. The presence of at least two positive observation signs yielded a Se of 0.50, Sp of 0.97, PPV of 0.86, and NPV of 0.81.

Conclusions DKS is frequently observed in neurology outpatients. It has low sensitivity but high specificity and PPV for CI diagnosis. It does not require additional consultation time, and its use can be recommended in combination with other observation-based signs.

Keywords Anosognosia · Cognitive impairment · Diagnostic accuracy · Observation · Neurological examination

Introduction and objectives

Observation is an essential component of neurological examinations, and neurologists take into consideration several observation-based signs [1–3]. Some have demonstrated a capacity to assist in the diagnosis of cognitive impairment (CI) or dementia, including attending alone (AA) [4], head turning sign (HTS) [5], and verbal repetition (VR) [6], offering immediate information without adding to the consultation time.

AA and its opposite “attending with” (AW) [7, 8] indicate whether or not the patient attends alone. Patients who have memory complaints that are not related to a purely amnestic problem (the “worried well”) more frequently attend on their own [9]. Various studies have found AA to be diagnostically useful to rule out dementia [4, 9] and CI [7, 8, 10–12].

HTS is positive when patients turn their head towards caregivers for help. It can be a clinical marker of Alzheimer’s disease in the differential diagnosis with other neurodegenerative disorders [13, 14]. Larner’s group defined head turning to seek help as positive when patients are asked about the reason for the consultation but not while engaged in cognitive tests, and they reported low sensitivity (Se) and high specificity (Sp) for CI when this definition was applied [5]. In other studies, the Se and Sp values were found to vary according to the method used for recording this sign and cultural differences [7, 8, 10, 15].

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VR is defined by the repetition of statements, stories, or questions during the consultation. A retrospective descriptive analysis was conducted on the frequency and severity (quantitative and qualitative) of this sign in patients with mild-to-moderate Alzheimer's disease [6]. However, we have found no prospective study that evaluated its diagnostic accuracy in a quantitative manner.

Patients are sometimes unaware of the reason for consultation with neurologists, and we have called this the "Don't know" sign (DKS). Observation-based signs favor an active approach to CI detection by clinicians [16], and we hypothesized that the DKS may also be useful in the diagnosis of CI. The objectives of this study were to define the DKS, to estimate its prevalence among patients referred to a neurology clinic, and to compare its diagnostic accuracy for CI with that of other observation-based signs.

Design, participants, and methods

All consecutive patients seen for the first time and for any reason by one of six consultant neurologists during a 5-month period (June to October 2018) were prospectively enrolled in the study. The settings were a general neurology consultation (referrals from primary care and other specialties) and a specific cognitive behavioral consultation, both in the Neurology department of a public hospital in Andalusia. Follow-up visits were excluded.

At the consultation, the patient was welcomed and invited to sit at the desk directly in front of the neurologist, who first asked the patient about the reason for the consultation. This question was always addressed to the patient, ignoring any spontaneous responses by caregivers/companions (henceforth caregivers), who always sat beside the patient and was not directly opposite the neurologist. DKS was considered positive if the patient did not respond or gave an incorrect response. The following DKS modalities were defined:

- Aware of not knowing: "I don't know", "I can't remember", or similar
- References to caregiver: "She/he will tell you", "She/he knows", or similar
- A complaint other than the reason for referral: stomachache, general malaise, or others
- Negation: "Nothing", "I'm fine", or similar
- Other: mutism, reference to person(s) not present, among others

The neurologists also observed the behavior and discourse of patients during the interview for the purpose of scoring the observation-based tests under study. We ensured that a positive result had the same meaning for all signs by using the AW (attends with another person) rather than the AA sign, even though the exceptional situation is that the patient attends alone [7]. HTS was considered positive even when the patient turned his head towards the caregiver/companion only once during questions about the complaint [7]. VR was considered positive when the patient repeated a statement or concept without being asked to do so. Although the neurologist was evidently not blinded to the above information, it was not considered in the diagnosis of cognitive impairment to reduce the incorporation bias.

The cognitive status of participants was evaluated by determining the Global Deterioration Scale (GDS) score [17], based on a combination of clinical history, caregiver interview (when available), and the results of cognitive tests, especially but not solely the Phototest [18, 19], Mini-Cog [20], and Semantic Verbal Fluency test [21], validated in our setting for CI detection. CI was clinically defined by a GDS score ≥ 3. The diagnostic accuracy achieved by these methods was compared with that obtained using the results of DKS, AW, HTS, VR, and different combinations of these observation-based signs. The STARD checklist for reporting diagnostic accuracy studies was followed [22], and Se, Sp, PPV, and NPV were determined by cross tabulation. Confidence intervals for Se, Sp, PPV, and NPV were established by using EPIDAT 4.2.

Patients with missing or incomplete GDS data were excluded from the analysis of test accuracy values, but the prevalence of the sign was calculated before their exclusion.

Results

The study included 673 consecutive patients new to our neurology outpatient unit: 415 (61.7%) were female, and the mean $\pm$ SD age was 59.3 ± 20.2 years, ranging from 14 to 97 years. The DKS was positive in 94 patients (14.0%).

After excluding 3 patients for missing GDS data, 670 were included in the accuracy analysis. Table 1 and Fig. 1 display data on their sex, age, consultation setting, main complaint, and the presence of signs under study.

A positive DKS correlated well with the GDS score (Fig. 2), showing a Cramer's V of 0.57 ($p < 0.001$) and (GDS-dependent) Eta coefficient of 0.56.

The distribution of different DKS modalities is depicted in Fig. 3.

Table 2 summarizes the Se, Sp, PPV, and NPV obtained for observation-based signs (AW, HTS, VR, DKS) and their combination.

Table 1 Characteristics and prevalence of signs in the sample

	CI (GDS ≥ 3)	No CI (GDS 1–2)	Total
Number of patients	205	465	670
Sex, female (n; %)	115; 56.1%	299; 64.3%	414; 61.8%
Age (mean ± SD)	75.1 ± 11.5	52.3 ± 19.3	59.3 ± 20.2
Consultation settings			
General neurology (n; %)	117; 57.1%	429; 92.3%	546; 81.5%
Mixed settings (n; %)	32; 15.6%	26; 5.6%	58; 8.7%
Cognitive behavioral (n; %)	56; 27.3%	10; 2.2%	66; 9.9%
Main complaint			
Cognitive complaints (n; %)	170; 82.9%	41; 8.8%	211; 31.5%
Other (n; %)	35; 17.1%	424; 91.2%	459; 68.5%
Presence of signs in CI, No CI, and Total groups			
AW (+) (n; %)	198; 96.6%	309; 66.5%	507; 75.7%
HTS (+) (n; %)	49; 23.9%	6; 1.3%	55; 8.2%
VR (+) (n; %)	37; 18.0%	3; 0.6%	40; 6.0%
DKS (+) (n; %)	84; 41.0%	10; 2.2%	94; 14.0%

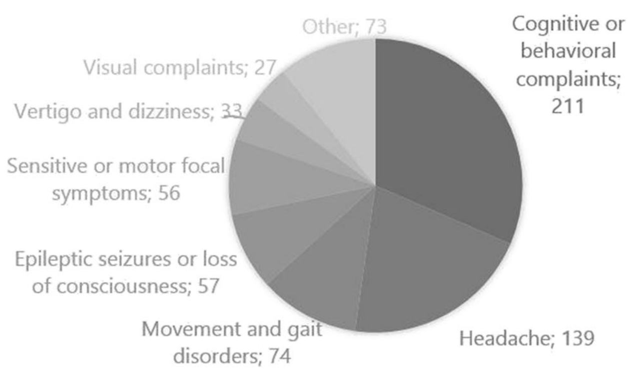


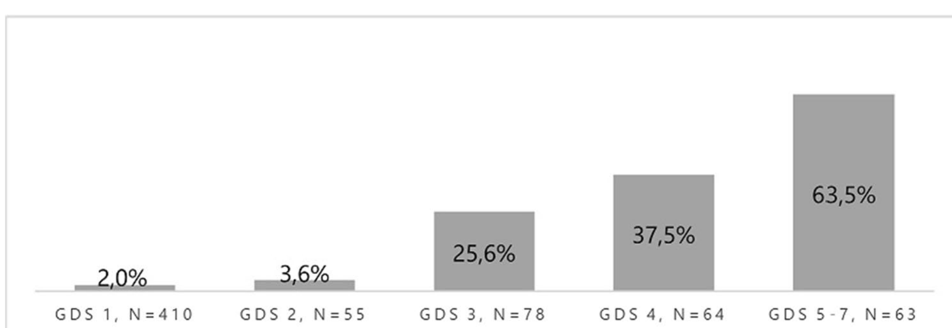
Fig. 1 Frequency of main complaints

Discussion

This study found that a novel observation-based sign, DKS, is very specific for the presence of CI and yields a high PPV among patients referred to a neurology clinic, similar to the values obtained using HTS and VR. In other words, CI is very likely when the DKS is positive, even more likely when two of these three signs are positive, and almost certain when they are all positive. High sensitivity and NPV were observed for AW, in line with previous results [4, 7, 9, 11] and confirming the usefulness of a negative AW sign, which reflects the very low likelihood of CI in patients who attend neurological consultancies on their own (AA).

The sensitivity of DKS was low, although higher than that of HTS and VR in our setting. We did not reproduce the moderate sensitivity of HTS reported in previous studies [5, 7], likely due to a less consistent methodology, given that we did not systematically place the caregiver 1 m behind the patient [15]. The low sensitivity of VR may be explained by the nature of the consultation, which predominantly consisted of responses to direct questions, with scant opportunity for free discourse; in addition, this sign requires constant observation, unlike

Fig. 2 Proportion of patients with positive DKS in GDS groups. GDS 5–7 are grouped to obtain a more comparable number of patients among groups



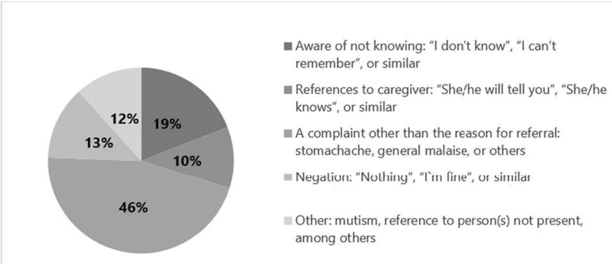


Fig. 3 Proportion of DKS modalities

DKS or AW. No quantitative analysis of the VR sign has been published for comparison.

Regarding the reason of consultation, cognitive complaints were very common in our sample (31.5%). We could identify three explanations for this. First, although most of our patients were seen in general neurology consultation (81.5%), the remaining came to specific clinics for cognitive complaints. Secondly, we are recording here the reason of consultation without later analysis of the underlying disorder; therefore, mood disorders could be included if they presented as cognitive symptoms. Finally, neurology clinics are the main resource for these symptoms in our settings, as geriatrics clinics are absent and psychiatry clinics do not address them. This has led to high prevalence of cognitive complaints in general neurology settings as registered and analyzed elsewhere [23].

Care should be taken to ensure that the methodology used in this study is followed in further research on its usefulness and in its clinical application to avoid the problem of inconsistent operationalization encountered in previous studies [8, 15]. There is also a need to address cultural factors.

The majority of the present patients attended a general neurology consultation, indicating that this sign is not only frequent in patients consulting for memory problems, who are the usual subjects in research on observation-based signs. The external validity of this study is supported by its naturalistic approach, with minimum exclusions.

The main limitation of this study is that the same neurologist who evaluated the presence of DKS also determined the GDS score in the same consultation, implying a risk of incorporation bias. In addition, although data from the medical history, caregiver interview, and select brief cognitive tests have consistently been associated with a neuropsychological diagnosis of CI [18, 24], further research using an independent gold-standard diagnosis of CI is warranted to verify and expand these results. Furthermore, there was no video recording and inter-rater reliability could not be assessed, another improvement to consider in further studies.

We have focused on the observation of the sign, and, although we consider anosognosia and memory impairment as the main reasons for its presence, further research with a different approach would be needed to define the neurobiology of the sign.

In conclusion, the DKS can be recommended to increase the pretest likelihood of CI detection in patients with memory or other cognitive complaints. It requires no additional consultation time and has demonstrated high Sp value and, in the present setting, a high PPV. The diagnostic accuracy of DKS for CI is comparable to that of other observation-based tests, and optimal results can be obtained by their combined use. In this way, CI can be expected if a patient does not attend alone and either DKS, HTS, or VR is also observed. Awareness of observation-based signs encourages general neurologists and primary care physicians to adopt a proactive approach to the early detection of CI.

Table 2 Parameters of diagnostic accuracy for observation-based signs and their combination

Sign	Se	Sp	PPV	NPV
AW	0.97 (0.94–0.99)	0.34 (0.29–0.38)	0.39 (0.35–0.43)	0.96 (0.92–0.99)
HTS	0.24 (0.18–0.30)	0.99 (0.98–1.00)	0.89 (0.80–0.98)	0.75 (0.71–0.78)
VR	0.18 (0.13–0.24)	0.99 (0.99–1.00)	0.93 (0.83–1.00)	0.73 (0.70–0.77)
DKS	0.41 (0.34–0.48)	0.98 (0.96–0.99)	0.89 (0.83–0.96)	0.79 (0.76–0.82)
At least 1 sign	0.98 (0.95–0.99)	0.33 (0.29–0.38)	0.39 (0.38–0.41)	0.97 (0.94–0.99)
At least 2 signs	0.50 (0.43–0.57)	0.97 (0.94–0.98)	0.86 (0.80–0.91)	0.81 (0.79–0.83)
At least 3 signs	0.24 (0.18–0.30)	1.00 (0.99–1.00)	0.98 (0.87–1.00)	0.75 (0.73–0.76)
4 signs	0.07 (0.04–0.12)	1.00 (0.99–1.00)	0.94 (0.66–0.99)	0.71 (0.68–0.75)

Author contribution Cristóbal Carnero-Pardo: conceptualization (lead), methodology (equal), data collection (equal), formal analysis (supporting), review and editing (equal). Virginia Guillén Martínez: data collection (equal), review and editing (equal). José Antonio Medina Gámez: data collection (equal), review and editing (equal). Iago Rego-García: methodology (equal), data collection (equal), formal analysis (lead), writing — original draft (lead); review and editing (equal). Carmen Valderrama Martín: data collection (equal), review and editing (equal). Rosa Vílchez Carrillo: data collection (equal), review and editing (equal).

Availability of data and material Available in soft copy upon request.

Code availability Not applicable.

Declarations

Conflict of interest None.

Ethical approval None.

Informed consent None.

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