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Research Article

Transcranial Sonography for the Diagnosis of Parkinson's Disease: Cost-effectiveness Revision

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Abstract

The diagnosis of Parkinson's disease is based mainly on clinical criteria and is assisted by support methods. A review of cost-effectiveness of transcranial sonography was conducted as a diagnostic test for Parkinson's disease. They analyzed three systematic reviews with meta analysis, five clinical practice guidelines and four coverage policies. No studies were found that evaluate the therapeutic impact and safety of transcranial sonography in Parkinson's disease. With a moderate quality of evidence, a lower net benefit from the diagnosis was observed, given that it only allows the differentiation of two large groups: degenerative parkinsonism and non-degenerative entities. The cost-effectiveness and the budget impact are uncertain. Its consideration within the diagnostic algorithm in clinical practice guidelines is heterogeneous. The consulted health financing agents do not include it among their coverage policies. With the information available it is not possible to make a recommendation for its routine use.

Keywords:

Parkinson's disease – Parkinsonian disorders – Essential tremor – Sonography – Substantia nigra – Diagnosis – Cost-effectiveness analysis – Review.

Introduction

Parkinson's disease (PD) is a chronic and progressive pathology caused by the neuronal degeneration of the black substance (SN), which leads to a decrease in dopamine levels and the subsequent appearance of classic motor symptoms. (1)

The etiology remains unknown and multifactorial. The prevalence is approximately 0.3% in the general population. It increases with age, reaching 2% in those over 60 years of age and more than 4% in those over 80 years of age. After Alzheimer's disease, it is the second neurodegenerative disease in adults, with an incidence of 8-18/100,000 people/year. (23)

The differential diagnosis of PD is extensive and constitutes a challenge, mainly in the first stages of the

disease. The international Parkinson and movement disorder society (MDS), considers that its clinical criteria validated in 2018 are the gold standard for the diagnosis of PD, with a precision that reaches 92.6%. (4,5) In a systematic review with meta analysis of the year 2016, it was demonstrated that the evaluation of patients by a specialist in movement disorders, compared to the histopathological study, has an accuracy of 84% for the diagnosis of PD. (6)

The images of computed tomography by emission of single photon of the striatal dopamine transporter (DaTScan) can be useful for patients in whom the clinical diagnosis is not clear. (3, 7) Furthermore, confirmation of cardiac sympathetic denervation in metaiodobenzylguanidine (MIBG) scintigraphy and the demonstration of olfactory loss can be considered as support for the diagnosis of PD. (4)

In Argentina, transcranial sonography (TCS) is frequently used to look for hyperechogenicity of the substantia nigra (SN+) in the diagnosis of PD, although its clinical value is unclear and controversial.

Ultrasound uses high frequency sound waves and reproduces images of the inside of the skull. There is no exposition to ionizing radiation associated. (8) The test consists of the application of a transducer on the temporal scale, on the orbitomeatal line on both sides, with a variable inclination in the mesencephalic observation planes (SN, raphe and red nucleus) and diencephalic (lateral ventricles, third ventricle, basal ganglia). It is performed with the patient in a supine position, with the head elevated approximately 30 degrees. The hyperechogenicity of the substance black is defined as an enlargement of the echogenic area of the mesenchymal SN attributed to iron deposit. The cutoff point can vary and is generally considered greater than 0.20 and 0.30 cm2. (9) The SN+ is found up to 10% of the healthy population. (10) Among the vantages of ETC are low cost of technical equipment, ample availability, non-invasiveness, repeatability and transportability. The main limitations of ECT are the dependence on the experience of the examiner and an insufficient temporal window. This may limit its application in 5-20% of patients in general, reaching figures of 15-60% in elderly women and Asian patients. (9)

The objective of this revision is to evaluate the evidence available about the performance of the diagnosis, the effectiveness, security and aspects related to the policies of coverage of the use of TCS for the initial diagnosis of patients with suspicion of Parkinson's disease.

Materials and Method

A search was conducted until the month of February 2023 in the main databases of bibliographic data in generic internet search engines, and health financiers.

It prioritized the inclusion of systematic revisions (SR), randomized controlled clinical trials (RCT), health technology evaluations (HTE), economic evaluations (EE), clinical practice guidelines (CGP) and coverage policies.

In Pub Med the following search strategy was used:

(Parkinson Disease [Mesh] OR Parkinson's disease[tiab] OR idiopathic Parkinson's disease[tiab] OR PD[tiab]) AND (Ultrasonography [Mesh] OR transcranial sonography[tiab] OR transcranial brain sonography[tiab] OR transcranial Doppler sonography[tiab]] OR TCS[tiab] OR ultrasound[tiab]) AND (Systematic Review[sb] OR Systematic Review[tiab] OR Meta-Analysis[pt] OR Meta-Analys*[tiab] OR "Cochrane Database Syst Rev[ta] OR Metaanalysis[tiab] OR Metanalysis[tiab] OR (MEDLINE[tiab] AND Cochrane[tiab]) OR Guideline[pt] OR Practice Guideline[pt] OR Guideline*[ti] OR Guideline*[tiab] OR Consensus[tiab] OR Recommendation*[ti] OR Randomized Controlled Trial[pt] OR Random*[ti] OR Controlled Trial*[tiab] OR Control Trial*[tiab] OR Technology Assessment, Biomedical[Mesh] OR Technology Assessment[tiab] OR Technology Appraisal[tiab] OR HTA[tiab] OR Overview[ti] OR (Review[ti] AND Literature[ti]))

The name of the technology and its synonyms and/or the pathology were searched in the International HTA Database (https://database.inahta.org/), Regional Base of Health Technology Assessment Reports in the Americas (BRISA, https://sites.bvsalud.org/redetsa/brisa/), Trip database and on the websites of health funders and scientific societies, as well as on internet search engines.

The inclusion criteria are detailed in Table 1. The inclusion criteria were unavailable full texts, duplicates, without explicitly naming the technology, and narrative reviews.

The quality of the evidence was based on the GRADE classification (Grading of Recommendations Assessment, Development and Evaluation). The net benefit (resulting from the benefit and the adverse effects) was based on the IQWiG classification system (from the German, InstitutsfürQualität und WirtschaftlichkeitimGesundheitswesen). The analysis of Cost-effectiveness and budgetary impact was

based on the classification developed by Institute of Clinical and Health Effectiveness (IECS). (11–13) (See Annex)

Table 1. Inclusion criteria. PICO asks.

Population	Patients with suspicion of Parkinson's disease.
Intervention	Transcranial sonography as initial diagnostic method.
Comparator	A: Diagnosis by clinical criteria. B: SPECT, PET. C: Medication test (L-dopa/apomorphine), smell test, cardiac scan, neuropathological study.
Results (in descending order of importance)	Therapeutic impact: mortality, quality of life, improvement in UPDRS - Hoehn and Yahr scales, initiation of treatment from diagnosis. Safety: number of deaths associated with the test, incidence of serious adverse events. Diagnostic precision: sensitivity, specificity, predictive capacity of the test.(**)
Design	Systematic reviews and meta-analyses randomized controlled clinical trials, technology evaluation reports, economic evaluations, clinical practice guidelines, coverage policies, recommendations of scientific societies.

(**) Predictive capacitance of the test: Analysis strategy that consists of graphically representing the pairs (1-specificity, sensitivity) obtained by considering all the possible cut-off values of the test, obtaining an ROC curve. The area under the curve (AUC) allows comparisons between different diagnostic tests, independent of the prevalence of the disease in the reference population. (14) According to the AUC value, the discriminative capacity of the diagnostic test is deduced, being excellent for AUC ≥ 0.9; good for AUC ≥ 0.8 and < 0.9; fair for AUC ≥ 0.7 and < 0.8; poor for AUC ≥ 0.6 and < 0.7; and poor for AUC ≥ 0.5 and < 0.6. In general, an AUC ≥ 0.8 is considered acceptable. (15)

Results

They included three SRs with meta analysis, five CPGs, and four TCS coverage policy reports for the diagnosis of Parkinson's disease.

Effectiveness

Heim et al., published in 2022 a systematic review with meta-analysis to evaluate the diagnostic accuracy of transcranial ultrasound for the differential diagnosis of PD compared to essential tremor (ET). (16) They analyzed 18 studies that included 1264 patients with PD and 824 with ET. All studies included only patients with sufficient temporal bone window. The meta-analysis showed sensitivity of 84.6% (95% CI: 79.4–88.6%) and specificity of 83.9% (95% CI: 78.4–88.2%) for ET in the differential diagnosis. of PD versus ET. The sensitivity analysis revealed a similar diagnostic accuracy compared to the primary meta-analysis, with a sensitivity of 82.1% (95% CI: 75.4–87.2%) and a specificity of 79.1% (95% CI: 68.8–86.6%), respectively. The power to discriminate patients with PD and ET was good, with area under the ROC curve of 0.84 (95% CI: 0.78–0.89). An analysis of subgroup that included 107 patients with PD and 62 patients with ET and compared the properties of ETC and DaTScan for differential diagnosis between both pathologies. There is evidence of sensitivity of 84.1% (95% CI: 75.9–89.9%) and specificity of 91.9% (95% CI: 82–96.6%) for TCS; and sensitivity of 90.7% (95% CI: 83.5–94.9%) and specificity of 96.8% (95% CI: 88–99.2%) for DaTScan. Application of the Quality Assessment of Diagnostic Accuracy Studies-version 2 (QUADAS-2) tool revealed a high risk of bias with respect to the methodological quality of the study patient selection, since all were treated in specialized outpatient services and only patients with sufficient temporal bone window were included in the final analysis.

Tao y cols., published in 2019 a systematic review with meta analysis to evaluate the diagnostic precision of the hyperechogenicity of the black substance via transcranial echography for the diagnosis of Parkinson's disease. (17) They analyzed 39 studies (two retrospectives, six prospective and 31 cases and controls) that included 3123 patients with PD, 2268 healthy controls and 870 with other parkinsonism.

The sensitivity was 84% (IC 95%: 81–87%) and the specificity was 84% (IC 95%: 80–88%) to differentiate Parkinson's disease from healthy controls or patients with other parkinsonian syndromes. Furthermore, PD patients exhibited a significant increase in substantia nigra areas compared with healthy controls (0.14 [0.12–0.16], $p < 0.0001$) and with other parkinsonian syndromes (0.11 [0.08 –0.13], $p < 0.0001$)" In the analysis of subgroups, it was shown that sensibility, specificity, area of black substance and diagnostic precision were consistent in studies with different control groups, study designs, sample sizes, geographical locations and patient age groups. .

Sensitivity and specificity were most beneficial in studies with a high cut value (>0.2 cm2) and high frequency ultrasound equipment. However, sensitivity was low in assays with lower cutoff values (<0.2

cm2). Sensitivity and specificity were low in assays with low frequency.

An analysis of sensitivity was performed, excluding one study at a time and calculating sensitivity and specificity for the rest of the studies. This analysis revealed that none of the individual studies significantly influenced sensitivity and specificity. The first ranged between 83% (95% CI: 80-86%) and 85% (95% CI: 82-87%), and the second ranged between 83% (95% CI: 80-86%) and 85%.(95% CI: 81-88%).

The power to discriminate PD patients from healthy controls or other parkinsonian syndromes was excellent, with an area under the ROC curve of 0.91 (95% CI: 0.88-0.93). A high heterogeneity was detected in the estimates (general heterogeneity I2=98.7%; sensitivity I2=89.1%; and specificity I2=92.1%). No significant publication bias was observed when evaluating the funnel plot and the Egger test (p = 0.22).

Shafiessabet et al., published in 2017 a systematic review with meta analysis to evaluate the diagnostic value of echography of the black substance to differentiate PD from atypical parkinsonism and ET. (18) They analyzed 71 articles that included 5730 patients, of which 4494 were PD, 594 atypical parkinsonism (AP) and 642 ET.

The combined prevalence rate of hyperechogenicity was 84% (95% CI: 80-87%) in PD, 28% (95% CI: 20-36%) in PA and 15% (95% CI: 7-23%) in ET. Hyperechogenicity of the substantia nigra (SN+) presented sensitivity of 75% (95% CI: 60-86%), specificity of 70% (95% CI: 55-81%) to differentiate PD from AP; and sensitivity of 78% (95% CI: 69-85%) and specificity of 85% (95% CI: 77-91%) to differentiate PD from ET. The power of hyperechogenicity of the substantia nigra, evaluated by TCS, to discriminate patients with essential tremor PD was fair, with area under the ROC curve 0.78 (95% CI: 0.63-0.88). The power of hyperechogenicity of the substantia nigra, evaluated by TCS, to discriminate patients with PD from atypical parkinsonism was fair, with area under the ROC curve 0.75 (95% CI: 0.5-0.9).

The positive likelihood ratio (LR) was 5.21 in Parkinson's disease vs. essential tremor. The positive likelihood ratio (LR) was 2.46 in Parkinson's disease vs. atypical parkinsonism. Deducing that SN+ evaluated by transcranial ultrasound increases the post-test probability of PD diagnosis five times compared to ET; and increases the post-test probability of PD diagnosis twice compared with PA. Overall heterogeneity between studies and outcomes was moderate/high.

Costs

The TCS has an approximate price of ARS 9,800 (February/2023 Argentine pesos), equivalent to USD 51 (February/2023 US dollars). (19,20)

Economic evaluations and health technology evaluations.

No economic and health technology diagnostic tests were found on the surveyed platforms.

Coverage policies

The coverage policies of private funders in the United States were reviewed, and it was found that Cigna, a health funder, does not refer to the use of TCS in the diagnosis of PE.(21) On the other hand, Aetna mentions its use only in the context of research. (22) The lack of universal coverage policy in the United States can limit access to this technique for patients without medical insurance or with limited medical coverage.

Access to TCS may be limited due to cost, especially for those patients who do not have medical coverage. It is important to highlight that currently transcranial echography is not included in the Mandatory Medical Program nor is it recovered through the Unique Reimbursement System for Disease Management in Argentina. (23,24)

Clinical Practice Guides

The diagnostic criteria updated by the international society of Parkinson and movement disorders in 2018, the Canadian guide for PD in 2019 and the PD guide of the National Institute of Health and Care Excellence of the United Kingdom (NICE) in 2017, do not mention the use of this technology for the diagnosis of PD. (5,7,25)

The Spanish Society of Neurology in its 2019 guide of recommendations for Parkinson's disease recommends the use of TCS in the diagnosis of the disease, prior to the evaluation of specialists in movement disorders and in patients with uncertain diagnosis, assigning it a level recommendation 1A. (3)

In the diagnostic guide for Parkinson's disease published in 2013 by the European Academy of Neurology (EAN), in collaboration with the European Federation of Neurological Societies (EFNS) and the MDS, the

use of transcranial ultrasound is recommended for the differential diagnosis of atypical and secondary parkinsonism, as well as for the early diagnosis of the disease and the identification of patients at risk of developing it. Furthermore, it is suggested to use it in combination with other diagnostic tests. (10)

In Argentina, although there are no specific clinical practice guidelines that recommend the use of transcranial ultrasound for the diagnosis of Parkinson's disease, the technique is used in some specialized centers.

Discussion

To guide the diagnosis of Parkinson's disease, an algorithm is generally recommended that includes a comprehensive neurological evaluation, auxiliary tests such as the fat test, scintigraphy with metaiodobenzylguanidine (MIBG) or a therapeutic test with levodopa. (4,5)

In cases of uncertain diagnosis or patients with inconclusive clinical suspicion, transcranial ultrasound can be useful to improve diagnostic accuracy and rule out healthy patients with essential tremor or secondary parkinsonism. (6,9)

Although this technology is relatively economical and non-invasive, it is important to note that more studies are needed to evaluate its cost-effectiveness in the diagnosis of PD. Therefore, its use should be considered moderately, depending on local availability and the clinical needs of each patient. (10)

Conclusion

No studies were found that evaluate the therapeutic impact (mortality, quality of life, clinical improvement, initiation of treatment starting from diagnosis) and safety of transcranial ultrasound in Parkinson's disease. The evidence analyzed in terms of diagnostic precision, evaluated by the GRADE system, is considered moderate given that it comes from systematic reviews with meta analysis that presented high heterogeneity and high risk of bias.

According to the IQWiG classification, the evidence shows that transcranial ultrasound would produce a lower net benefit in terms of diagnostic performance, given that it only allows the differentiation of two large groups. On the one hand, degenerative parkinsonism included atypical parkinsonism and Parkinson's disease and on the other, non-degenerative entities such as essential tremor, secondary parkinsonism and

healthy controls. The cost-effectiveness and budget impact, based on IECS classification, are uncertain. In European guidelines, transcranial ultrasound is considered part of the Parkinson's diagnosis algorithm. The rest of the clinical practice guidelines surveyed do not mention the routine use of this technology for the diagnosis of PD.

Health financing agents consulted do not include it among their coverage policies for the diagnosis of this pathology. With the information available, it is not possible to make a recommendation for its routine use and other factors must be considered for its incorporation.

Conflicts of interest

There is no conflict of interest in relation to the contents of this document.

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