J Neurol (2009) 256:530–538
DOI 10.1007/s00415-009-0143-8

REVIEW

Annemarie M. M. Vlaar
Angela Bouwmans
Werner H. Mess
Selma C. Tromp
Wim E. J. Weber

Transcranial duplex in the differential diagnosis of parkinsonian syndromes

A systematic review

Received: 1 September 2008
Received in revised form: 1 September 2008
Accepted: 2 September 2008
Published online: 17 February 2009

A. M. M. Vlaar (✉) · A. Bouwmans · W. E. J. Weber, MD, PhD
Dept. of Neurology
University Hospital Maastricht
PO Box 5800
6202 AZ Maastricht, The Netherlands
Tel.: +31-43/387-5117
Fax: +31-43/387-7055
E-Mail: A.VLAAR@mumc.nl

W. H. Mess, MD, PhD
Dept. of Clinical Neurophysiology
University Hospital Maastricht
Maastricht, The Netherlands

S. C. Tromp, MD, PhD
Dept. of Clinical Neurophysiology
St. Antonius Hospital
Nieuwegein, The Netherlands

Abstract *Background* Transcranial duplex scanning (TCD) of the substantia nigra (SN) is increasingly used to diagnose Idiopathic Parkinson's Disease (IPD). Up until now 70 diagnostic studies have been published, not only on investigation of the SN, but also of the lenticular nucleus (LN) and the Raphe nuclei (RN). *Method* We systematically reviewed all diagnostic TCD studies in parkinsonian patients up to June 2008. *Results* We found 35 eligible studies. Of the 1534 IPD patients investigated in the 35 studies 200 (13 %) had an inconclusive SN-TCD. An increased echo-intensity of the SN was seen in 1167 (87 %) of the 1334 IPD patients, 276 (12 %) of the 2340 healthy controls and in 41 (30 %) of the 138 patients with an atypical parkinsonian syndrome (APS). On the contrary, a pathological LN-TCD was found more often in APS patients (79 %) than in IPD patients (23 %) and healthy controls (6 %). A decreased echo-intensity of the RN was found more often in depressed (46 %) than in non-depressed IPD patients (16 %). *Conclusions* SN-TCD accurately differentiates between patients with IPD and healthy controls, but not between patients with IPD and APS. LN-TCD is only moderate accurate to delineate IPD from APS, but combinations of SN- and LN-TCD may be more promising. RN-TCD has only marginal diagnostic accuracy in diagnosing depression in IPD and non-IPD patients. Before TCD can be implicated, more research is needed to standardize the TCD technique, to investigate the TCD in non-research settings and to determine the additional value of TCD compared with currently used clinical techniques like SPECT imaging.

Key words diagnosis · parkinsonism · idiopathic Parkinson's disease · ultrasonography · transcranial duplex scanning · depression

Abbreviations

APS	Atypical Parkinsonian Syndromes
DIP	Drug Induced Parkinsonism
ET	Essential Tremor
IPD	Idiopathic Parkinson's Disease
LN	Lenticular Nucleus
MSA	Multiple System Atrophy
PET	Positron Emission Tomography
PSP	Progressive Supranuclear Palsy
RN	Raphe Nuclei
SN	Substantia Nigra
SPECT	Single Photon Emission Computer Tomography
TCD	Transcranial Duplex Scanning
VP	Vascular Parkinsonism

JON 3143

Introduction

The diagnosis of Parkinson's disease (IPD) and other parkinsonian disorders, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP) or vascular parkinsonism (VP), is based on clinical criteria [1–5]. In patients with the essential clinical symptoms such as bradykinesia, rigidity, and resting tremor, diagnosis of IPD is usually straight forward; however early in the disease it can be difficult to differentiate among the various parkinsonian disorders purely on clinical grounds. In the early stages of the disease it can also be difficult to differentiate a parkinsonian tremor from an essential tremor (ET). The gold standard for the diagnosis of IPD is post-mortem neuropathological examination. Neuropathological studies have shown that even at end-stage disease the clinical diagnostic accuracy for IPD varies between 75–90 %, with MSA and PSP accounting for most false positives [3, 6, 7]. As prognosis and management differ considerably among the various parkinsonian syndromes an early correct diagnosis is of cardinal importance.

Several procedures and combinations of different techniques have been proposed to diagnose IPD [8–12]: olfactory and neuropsychological tests, biomarkers, DNA tests and functional imaging with MIBG scintigraphy, positron emission tomography (PET) or single photon emission computer tomography (SPECT). The SPECT scan is presently the most widely used diagnostic test for parkinsonian syndromes. Nevertheless, its diagnostic accuracy is still debated [13].

A recently developed diagnostic tool is transcranial duplex scanning (TCD). Using this technique Becker and colleagues were the first to report hyperecho-intensity of the substantia nigra (SN) in patients with Parkinson's disease [14]. Several studies found that 90 % of IPD patients show this SN hyperecho-intensity [14–18], which is presumably caused by an increased iron content [19]. Only in about 9 % of healthy individuals is increased echo-intensity found. TCD can also visualize the Raphe nuclei (RN) and the lenticular nucleus (LN). The echo-intensity of the LN is postulated to differentiate between IPD and other parkinsonian syndromes. Differences in echo-intensity of the RN are reported to be associated with depression in patients with or without parkinsonism.

Since the first report, numerous studies on the diagnostic accuracy of TCD in parkinsonian syndromes have been published, including a systematic review, which considered all papers published before 2003 [20]. Since several more research groups started TCD and the majority of the papers on this subject is published after 2003 we did an updated systematic review.

Technical aspects

TCD is a non-invasive, fast, and patient-friendly technique, which is employable at the bedside. Mostly, the technique is applied for the examination of the intracranial vessels [21].

Since 15 years TCD is also used to visualize other brain structures, such as the mesencephalon [22]. With TCD the echo-intensity of various brain structures can be studied. Changes in echo-intensity seem to reflect changes in tissue impedance due to glial reaction, alterations in cell density and iron content [14, 16].

TCD is performed by placing the ultrasound transducer on the temporal bone in front of the ear. In most patients (approximately 80–90 % [23]) the temporal bone window is appropriate to acquire a 2-dimensional image of the intracranial structures. Typically, a low-frequency phased array transducer is used with a frequency range of 1–4 MHz being focussed at a depth of 6–8 cm. The depth range ideally is chosen to allow for the visualization of the contralateral side of the skull. The mesencephalon becomes visible as an echolucent, butterfly-shaped structure, surrounded by the basal cisterns characterized by a higher echo-intensity. Normally, the mesencephalon has a predominantly homogeneous aspect; in most cases a small hyperechogenic stripe can be discerned within the area of the substantia nigra (SN). However, in up to 90 % of the IPD patients the SN is clearly visible due to its large hyperecho-intense area as compared to the surrounding brainstem tissue.

Other brain structures like the lenticular nucleus (LN) and the Raphe nuclei (RN) can be visualized by TCD as well. The LN are visible in an axial section at the level of the thalamus. The LN is only discernable when its echo-intensity is abnormally increased compared with the surrounding brain parenchyma. An increase in echo-intensity of one or both of the LN might differentiate between APS and IPD [20, 24, 25].

Finally, the RN are visible in the same axial section as the SN. Normally the RN are visible because they are hyperecho-intense compared with the adjencent brainstem parenchyma. A decrease in the echo-intensity of the RN is reported to be associated with depression in both patients with and without parkinsonism [23, 26].

Different scorings systems are used by different research groups; however the various methods agree on the main points. Generally the echo-intensity of the SN is evaluated by ipsilateral TCD examination. The SN-TCD is scored abnormal if the SN is pathological at least at one side (uni- or bilateral).

The echo-intensity of the SN can be judged qualitatively or quantitatively. In the qualitative way the SN can be scored by judging whether or not a typical hyperecho-intensity in the area of the substantia nigra is present. Most investigators, however, used the quantitative method: measuring the area of hyperecho-intensity by

encircling the hyperintense area. Normal values depend on the ultrasound device which used, but approximately an area of $< 0.2\,cm^2$ is defined as normal and an area of $> 0.25\,cm^2$ as pathological [17, 18, 27]. For the quantitative method excellent intra- and inter-observer agreement has been reported with kappa values of 0.80–0.85 [16, 18, 28–30].

The LN as well the RN are always scored qualitatively (hyper-, iso-, or hypoecho intense).

Systematic review of the literature

We systematically reviewed the literature by searching Ovid Medline databases and cross-referenced clinical trials published in this field until June 15, 2008. Both medical subjects headings (MESH) terms and text words were used: 1) ultrasound, sonography or duplex scanning, 2) substantia nigra (SN), Raphe nuclei (RN), lenticular or lentiform nucleus (LN) and 3) parkinsonian, parkinsonism, IPD, MSA, PSP, ET or APS.

Two investigators (AV, AB) screened the full text of potentially relevant articles. Papers were only included into the review if information on the following items was supplied: 1) patient population, 2) ultrasound system applied, 3) TCD procedures of assessment and quantification of echo-intensity, 4) number of true positive, false positive, true negative and false negative TCD results with the clinical diagnosis as the golden standard.

Additionally, we mentioned the number of sonographers, if the sonographers were blinded for the clinical diagnosis and if the included patients were diagnosed or yet undiagnosed.

Papers were excluded if: 1) the full article was not available, 2) the language was other than English or German, 3) brain structures other than the SN, LN or RN were studied, 4) and if studies did not include patients with neurodegenerative parkinsonism (IPD, APS, i.e. MSA, PSP, diffuse Lewy body disease, corticobasal degeneration), patients with secondary parkinsonism (ET, VP, drug-induced parkinsonism (DIP)) or patients with ET, healthy controls and patients with depression.

Data extraction and analysis

The studies were sorted into three categories, either studying the SN, LN or the RN. The number of patients with a normal and abnormal echo-intensity of, respectively, the SN, LN and RN are given in Tables 1–3. We used cut-off points defined by the original authors. A TCD was considered inconclusive if either there was an inappropriate temporal bone window or the sonographer judged the target structure as borderline hyperecho-intense. Sensitivity and specificity were calculated for each brain structure and patient category separately. The following patient categories were studies: 1) neurodegenerative parkinsonism A) IPD and B) APS (MSA, PSP, diffuse Lewy body disease, corticobasal degeneration), 2) patients with non-degenerative forms of parkinsonism, i.e. vascular, drug-induced, infectious, 3) patients without parkinsonism (ET, healthy controls).

Results

Overview

The Medline search resulted in 68 hits. We found no additional clinical studies searching the Cochrane and Embase databases. Cross-reference searching added another four relevant trials. Of these 72 studies we excluded 37. The reasons for exclusion for as follows: for 18 studies only an abstract existed, 2 articles did not fulfill the language criteria, 10 papers did not deal with the diseases mentioned above, and in 7 articles we were not able to derive the number of true positive, false positive, true negative and false negative findings.

In the 35 trials left, either one or several brain structures (SN, LN and RN) were investigated. In total, 31 dealt with the SN, 10 with the LN and 7 with the RN (Tables 1–3).

TCD of the substantia nigra

Results are given in Table 1. Only 23 of the 31 studies mentioned the percentage of patients in which the authors experienced difficulties judging the SN-TCD, either because of an inappropriate temporal bone window or an atypical form of the hyperecho-intensity. The percentages in which the SN-TCD was inconclusive ranged from 0 % to 64 %.

In the majority of cases the SN-TCD was regarded as abnormal if the SN showed a pathological signal at least at one side. However, some authors calculated the mean of both sides [31–33]. Mostly, the area of increased signal intensity was measured to estimate whether the SN was normal or not.

The incidence of a pathological SN-TCD varied remarkably between the different parkinsonian syndromes as shown in Table 1. Of the 1334 IPD patients 1167 (87 %, range 48–100 %) had an increased echo-intensity of the SN. In patients with APS this hyperecho-intensity was seen less frequently, namely in 41 of the 138 (30 %; range 0–100 %). In ET, VP and DIP the prevalence of a hyperecho-intense SN was even lower: 13 of the 112 (12 %) ET patients, 6 of the 30 (20 %) VP patients and in 0 of the 3 DIP patients. In healthy controls SN hyperecho-intensity was found in only 276 of the 2340 (12 %, range 0 %–20 %) individuals.

Table 1 Transcranial duplex scanning (TCD) of the Substantia Nigra (SN) [14–16, 18, 24, 25, 28–34, 36, 38–42, 46, 47, 49, 51–58, 61]

Author	Blind Observer	Number observers (total involved in parts of the procedure)	Equipment	Patients: – already diagnosed (AD) – undiagnosed patients with follow-up (UD)	Threshold (cm^2)	SN-TCD in IPD			SN-TCD in APS			SN-TCD in ET			SN-TCD in healthy controls		
						N = IPD	Number (%) inconclusive TCDs	Number (%) abnormal TCD's of the number conclusive TCD's	N = APS	Number (%) inconclusive TCDs	Number (%) abnormal TCDs of the number conclusive TCDs	N = ET	Number (%) Inconclusive TCDs	Number (%) abnormal TCD's of the number conclusive TCDs	N = Controls	Number (%) inconclusive TCDs	Number (%) abnormal TCDs of the number conclusive TCDs
Becker '95 [14]	?	?	Siemens	AD	Visual	30	5 (17 %[b])	12 (48 %) of 25							30	2 (7 %[b])	0 (0 %) of 28
Behnke '05 [25]	?	1	Siemens	AD	0.20	102	23 (23 %[c])	78 (99 %) of 79	55	35 (64 %[c])	15 (75 %) of 20						
Berg '99 [18]	?	2	X	AD	0.25										330	29 (9 %[a])	26 (9 %) of 301
Berg '01 [41]	Yes	1 (–2)	Siemens	Diagnosed same day	0.20										93[d]	14 (15 %[a])	11 (14 %) of 79
Berg '01 [16]	Yes	2	Siemens	AD	0.19	112	9 (8 %[a])	94 (91 %) of 103									
Budisic '08 [28]	Yes	2	Aloka	AD	0.20	80	10 (13 %[a])	64 (91 %) of 70				30	–	4 (13 %) of 30	80	10 (13 %)	7 (10 %) of 70
Doepp '07 [61]	Yes	1	Siemens	AD	0.20	46	2 % excluded before	36 (78 %) of 46				25	2 % excluded before	2 (8 %) of the 25	50	2 % excluded before	5 (10 %) of 50
Gaenslen [58]	Yes	1	Siemens	UD	0.20	43	0 (0 %)	39 (91 %) of 43	13	0 (0 %)	2 (15 %) of 13						
Godau '07 [31]	Yes	2	Siemens	AD	0.20										50	1 (2 %)	3 (6 %) of 49
Godau '07 [32]	Yes	1	Siemens	AD	0.20										45	3 (7 %)	7 (17 %) of 42
Huang '07 [30]	Yes	1	HP-4500	AD	0.20	90	10 (11 %[a])	54 (68 %) of 80							192	28 (15 %[a])	8 (5 %) of 164
Kim '07 [33]	Yes	1 (–3)	Philips5000	AD	0.20	43	8 (19 %[a])	29 (83 %) of 35							35	8 (23 %[a])	2 (7 %) of 27
Mijajlovic '08 [51]	Yes	1	Esaote	AD	0.20	30	X	28 (93 %) of 30							30	X	2 (7 %) of 30
Okawa '07 [38]	Yes	2	Toshiba	AD	Visual	98	35 (36 %[a])	52 (83 %) of 63	31	7 (23 %[a])	2 (8 %) of 24	19	6 (32 %[a])	0 (0 %) of 13	30	15 (50 %[a])	1 (7 %) of 15
Postert '99 [52]	Yes	1	Ultramark	AD	Visual										39[e]	X	4 (10 %) of 39
Prestel '06 [53]	Yes	1	Siemens	AD	0.20	42	8 % excluded before	36 (86 %) of 42							35	8 % excluded before	6 (17 %) of 35
Ressner '07 [54]	Yes	1	Esaote/ATL	AD	0.19	47	X	41 (87 %) of 47							39	X	2 (5 %) of 39
Ruprecht '03 [42]	Yes	1 (–2)	Siemens	AD	0.19	14	X	13 (93 %) of 14									
Schmidauer '05 [55]	?	1 (–2)	G. Electric	AD	0.20	20	X	19 (95 %) of 20							20	X	4 (20 %) of 20
Schweitzer '06[29]	Yes	2	Siemens	AD	0.20	16	X	13 (81 %) of 16									
Schweitzer '07[56]	Yes	1	Siemens	AD	0.25										1120[f]	X	173 (15 %) of 1120
Spiegel '06 [49]	Yes	1	Siemens	AD	0.19	53	1 (2 %[a])	43 (83 %) of 52									
Stockner '07 [57]	Yes	1 (–2)	G. Electric	AD	0.24	100	X	75 (75 %) of 100				44	X	7 (16 %) of 44	100	X	3 (3 %) of 100
Tsai '07[1] [36]	Yes	2	Philips4500	AD	0.24	80	20 % excluded before	67 (84 %) of 80							60	20 % excluded before	3 (5 %) of 60
Walter '02 [24]	?	1 ?	Siemens	AD	0.25	30	8 (27 %[b])	22 (100 %) of 22							30	5 (17 %[b])	2 (8 %) of 25
Walter ' 03 [15]	Yes	1	Siemens	AD	0.25	25	5 (20 %[c])	19 (95 %) of 20	25	4 (16 %[c])	0 (0 %) of 21						
Walter '04 [39]	Yes	1	Siemens	AD	0.25				21	5 (24 %[b])	7 (44 %) of 16						
Walter '06 [34]	Yes	1	Siemens	AD	0.25	104	20 (19 %[c])	79 (94 %) of 84	14	3 (21 %[c])	11 (100 %) of 11						
Walter '07 [40]	Yes	1 (–3)	Siemens	AD	0.25	138	26 (19 %[c])	109 (97 %) of 112	43	10 (23 %[c])	4 (12 %) of 33						
Walter '07 [46]	Yes	1	Siemens	AD	0.25	90	18 (20 %[b])	70 (97 %) of 72							55	8 (15 %[b])	7 (15 %) of 47
Walter '07 [47]	Yes	1	Siemens	AD	0.25	101	22 (22 %[c])	75 (95 %) of 79									
Total						1534	200 (13 %)	1167 (87 %) of 1334	202	64 (34 %)	41 (30 %) of 138	118	6 (7 %)	13 (12 %) of 112	2463	123 (5 %)	276 (12 %) of 2340

IPD idiopathic Parkinson's disease; *APS* atypical parkinsonian syndromes such as multiple system atrophy, progressive supranuclear palsy; *ET* essential tremor; *TCD* transcranial duplex scanning; *SN* substantia nigra; *N* number

[1] 30 patients with vascular parkinsonism: 6/30 (20 %) had a positive SN-TCD

Inconclusive: [a] inappropriate temporal bone window; [b] borderline aberrant (or slightly or moderate); [c] both or not classified by authors controls; [d] 93 subjects older than 60 years without history of extrapyramidal disorder; [e] 39 control patients existing of: 17 healthy controls, 10 neuropathy, 6 headache, 2 myopathy, 1 radicular pain, 3 peripheral nerve lesion; [f] 1120 subjects older than 50 years without signs of IPD

Table 2 Transcranial duplex scanning (TCD) of the lenticular nucleus (LN) [15, 24, 25, 34, 39, 40, 46, 47, 52, 58]

Author	Blind observer	Number observers (total involved in parts of the procedure)	Equipment	Patients: – Already diagnosed (AD) – undiagnosed patients with follow-up (UD)	LN-TCD in IPD			LN-TCD in Healthy controls			LN-TCD in APS			LN-TCD in other disorders		
					N = IPD	Number (%) inconclusive TCDs	Number (%) abnormal TCDs of the number conclusive TCDs	N = Healthy	Number (%) inconclusive TCDs	Number (%) abnormal TCDs of the number conclusive TCDs	N = APS	Number (%) inconclusive TCDs	Number (%) abnormal TCDs of the number conclusive TCDs	N = other disorders	Number (%) Inconclusive TCDs	Number (%) abnormal TCDs of the number conclusive TCDs
Behnke '05 [25]	?	1	Siemens	AD	102	14 (14 %[a])	10 (11 %) of 88				55	5 (9 %[a])	36 (72 %) of 50			
Gaenslen [58]	Yes	1	Siemens	UD	43	4 (10 %[c])	14 (36 %) of the 39				13	1 (8 %[c])	9 (80 %) of 12			
Postert '99 [52]	Yes	1	UltramarkATL	AD				39	0 (0 %)	0 (0 %) of 39				49 Huntington	4 (8 %[a])	3 (7 %) of 45
Walter '02 [24]	?	1?	Siemens	AD	30	6 (20 %[c])	6 (25 %) of 24							30 NED[d]	3 (10 %[c])	5 (19 %) of 27
Walter '03 [15]	Yes	1	Siemens	AD	25	3 (12 %[b])	5 (23 %) of 22				25	3 (12 %[c])	17 (77 %) of 22			
Walter '04 [39]	Yes	1	Siemens	AD							21	5 (24 %[c])	14 (88 %) of 16			
Walter '06 [34]	Yes	1	Siemens	AD	31	6 (19 %[c])	16 (64 %) of 25				14	3 (21 %[c])	9 (82 %) of 11			
Walter '07 [47]	Yes	1	Siemens	AD	101	13 (13 %[c])	19 (22 %) of 88									
Walter '07 [40]	Yes	1 (–3)	Siemens	AD	138	13 (9 %[c])	31 (25 %) of 125				43	4 (9 %[c])	34 (87 %) of 39			
Walter '07 [46]	Yes	1	Siemens	AD	90	8 (9 %[c])	11 (13 %) of 82	55	0 (0 %)	6 (11 %) of 55				55 depression	5 (9 %)	11 (22 %) of 50
Total					560	67 (12 %)	112 (23 %) of 493	94	0 (0 %)	6 (6 %) of 94	171	21 (12 %)	119 (79 %) of 150	–	–	–

IPD idiopathic Parkinson's disease; *APS* atypical parkinsonian syndromes such as multiple system atrophy, progressive supranuclear palsy; *TCD* transcranial duplex scanning; *N* number; *SN* substantia nigra; *RN* Raphe nuclei
[a] inappropriate temporal bone window; [b] borderline aberrant (or slightly or moderate); [c] both or not classified by authors controls; [d] non-extrapyramidel discedees

Table 3 Transcranial duplex scanning (TCD) of the Raphe nuclei (RN) [26, 34, 46–48, 59, 60]

Author	Blind observer	Number observers (total involved in parts of the procedure)	Equipment	Patients: – Already diagnosed (AD) – undiagnosed patients with follow-up (UD)	RN-TCD in non-depressed IPD patients			RN-TCD in depressed IPD patients			RN-TCD in healthy controls			RN-TCD in depressed patients without IPD		
					N =	Number (%) inconclusive TCDs	Number (%) abnormal TCD of total number of conclusive TCDs	N =	Number (%) inconclusive TCDs	Number (%) abnormal TCD of total number of conclusive TCDs	N =	Number (%) inconclusive TCDs	Number (%) abnormal TCD of total number of conclusive TCDs	N =	Number (%) inconclusive TCDs	Number (%) abnormal TCD of total number of conclusive TCDs
Becker '94 [59]	Yes	2	Siemens	AD							20	7 (35 %[b])	0 (0 %) of 13	20	6 (30 %[b])	14 (100 %) of 14
Becker '95 [26]	Yes	1	Siemens	AD							40	11 (28 %[b])	0 (0 %) of 29	40	11 (28 %[b])	27 (93 %) of 29
Becker '97 [48]	Yes	1	Siemens	Diagnosed same time	17	6 (35 %[b])	1 (9 %) of 11	13	4 (31 %[b])	8 (89 %) of 9	30	12 (40 %[b])	1 (6 %) of 18			
Berg '99 [60]	Yes	2	Siemens	Diagnosed same time	11	3 (27 %[b])	0 (0 %) of 8	20	6 (30 %[b])	11 (79 %) of 14						
Walter '06 [34]	Yes	1	Siemens	AD	31	2 (6 %[a])	6 (21 %) of 29									
Walter '07 [46]	Yes	1	Siemens	AD	45	0 (0 %)	7 (16 %) of 45	45	0 (0 %)	17 (38 %) of 45	55	0 (0 %)	5 (9 %) of 55	55	0 (0 %)	29 (53 %) of 55
Walter '07 [47]	Yes	1	Siemens	AD	56	2 (4 %[a])	9 (17 %) of 54	45	2 (4 %)	15 (35 %) of 43						
Total					160	13 (8 %[c])	23 (16 %) of 147	123	12 (10 %[b])	51 (46 %) of 111	145	30 (21 %[b])	6 (5 %) of 115	115	17 (15 %[b])	70 (71 %) of 98

IPD idiopathic Parkinson's disease; *TCD* transcranial duplex scanning; *N* number; *SN* substantia nigra; *RN* Raphe nuclei
[a] inappropriate temporal bone window; [b] borderline aberrant (or slightly or moderate); [c] both or not classified by authors controls

TCD of the lenticular nucleus

Results are given in Table 2. The investigators of all 10 studies mentioned the percentage of patients in which they had difficulties to judge the echo-intensity of the LN. The percentages in which the LN-TCD was inconclusive ranged from 0 % to 24 %. Of the 150 APS patients 119 (79 %; range 72–88 %) had an increased echo-intensity of the LN. In IPD patients this hyperecho-intensity was seen less often, namely in 112 of the 493 (23 %, range 11–64 %) patients, with the remarkable exception of demented IPD patients: 64 % of these had a pathological LN-TCD [34]. In healthy controls this finding was seen in only 6 of 94 subjects (6 %, range 0–11 %).

TCD of the Raphe nuclei

Results are given in Table 3. In all 7 studies the percentage of patients with an inconclusive RN-TCD was mentioned and ranged from 0 % to 40 %. Fifty-one of the 111 depressed IPD patients (46 %, range 35–89 %) had a decreased echo-intensity of the RN in contrast to 23 of the 147 non-depressed IPD patients (16 %, range 0–21 %). In patients without IPD this difference was more pronounced: in depressed patients without IPD a decreased echo-intensity of the RN was much more common than in non-depressed healthy controls: 71 % (range 53–100 %) versus 5 % (range 0–9 %), respectively.

Discussion

In this review we included 35 papers on the diagnostic use of TCD in parkinsonian syndromes. The results are discussed separately for: A) the TCD technique in general, B) TCD of the substantia nigra, C) the lenticular nucleus, D) the Raphe nuclei.

The TCD technique in general

Studying the literature we found the following differences in TCD technique:

First, different research groups use different transducers, different measuring methods and cut-off points of normal values, causing varying sensitivity and specificity. To compare the results of these different studies, we applied a simplified semi-quantitative scoring system to the original data: abnormal, normal, or inconclusive. Consequently, lower sensitivity and higher specificity values were obtained than compared to the ones originally reported.

Second, we can not rule out that the same patient(s) that were used in one particular study were included in other studies of the same research group, i.e. that there is an overlap in patients.

TCD of the substantia nigra

Of the 1167 IPD patients examined in 31 different clinical studies, approximately 90 % had an increased echo-intensity of the SN. The sensitivity as compared with the final clinical diagnosis varied from 48 % to 100 %. The wide range can be explained by the different patient population under study, the use of various transducers and scorings methods by the different investigators.

The incidence of a pathological SN-TCD in patients with APS was considerably lower than in patients with IPD. Yet, the range was very large between studies and also depended on the subtype of APS. All 11 patients with diffuse Lewy body disease and 7 of the 8 patients with corticobasal degeneration had a positive SN-TCD [34–39]. A positive SN-TCD seemed to be more common in PSP (30 %, range 8–47 %) than in MSA (17 %, range 6–25 %) [15, 25, 38–40].

In all patients with APS, the number of inconclusive TCD examinations was higher than in patients with IPD. This finding was mostly attributable to difficulties in the interpretation of the ultrasound image and rarely due to an inappropriate bone window.

In 12 % of 2340 healthy controls SN hyperecho-intensity was found, suggesting a rather large number of false-positive findings. However, there is some evidence that the SN hyperecho-intensity in healthy controls is related to a slight motor impairment [41]. Additionally, earlier studies showed that PET or SPECT scans are also abnormal in up to 60 % of the asymptomatic patients with an abnormal TCD [17, 18, 42–44)]. Long-term follow-up studies are currently underway to evaluate if these asymptomatic subjects with an abnormal SN-TCD will develop IPD. Furthermore, from the literature there is indeed some evidence to suggest that a subset of ET patients is predisposed to developing idiopathic Parkinson's disease, possible explaining the fact that 12 % of the ET patients had an abnormal SN-TCD [45].

TCD of the lenticular nucleus

It appears that hyperecho-intensity of the LN is found quite often in APS (79 %), but considerably less often in IPD (23 %) and healthy controls (6 %). These findings suggest that TCD of the LN solely will not allow for the discrimination between IPD and APS in an individual patient, given the relatively low positive and negative predictive values. However, when combining the results of different insonated brain structures, the diagnostic accuracy could be improved considerably. An increased echo-intensity of the SN and a normal echo-intensity of the LN is strongly suggestive for the diagnosis of IPD [23, 25, 46, 47]. On the contrary, a normal SN echo-intensity and an increased intensity of the LN indicates MSA or PSP. Furthermore, a dilation of the third ventricle or

the frontal horn is postulated to be a predictor of PSP [40]. However, these results were obtained with post hoc analyses and their definitive diagnostic value remains to be determined in a long-term follow-up study with an 'intention-to-diagnose' principle.

TCD of the Raphe nuclei

Seven retrospective studies have been published about the difference of RN echo-intensity between IPD patients and controls with and without depression. Decreased RN echo-intensity was found more often in depressed patients (71 %) than in healthy controls without depression (5 %). Similarly, decreased RN echo-intensity was more common in IPD patients with a depression (46 %) than in IPD patients without depression (16 %).

Although the diagnostic accuracy of RN-TCD seems to be fairly high in non-IPD patients, RN-TCD is considerably less accurate in patients with IPD. Furthermore, the percentage of patients with doubtful findings or slightly decreased echo-intensity in the latter group is surprisingly high, with a maximum of 40 % in one study [48].

Conclusion

Compared to an earlier review considering the literature available until 2003 [23], our present up-to-date review confirms the high diagnostic accuracy of SN-TCD to differentiate patients with IPD from patients with ET and healthy controls. This accuracy is less for differentiating patients with IPD from those with APS. The diagnostic value of LN-TCD and RN-TCD appears to be lower than previously assumed.

We identified several methodological issues: lack of standardized TCD techniques, normal values and scoring systems, and the high percentage of subjects with an inconclusive TCD. More research is needed, especially in patients with as yet undefined parkinsonism. Moreover, these studies should ideally include neuropathological post-mortem investigation, or at least comparison with follow-up examinations and accepted techniques as SPECT or PET [49, 50]. These are essential to establish the clinical significance of SN-TCD.

Conflict of interest There are no financial or personal conflicts of interests.

Disclosure The authors report no conflicts of interest.

Documentation of author roles Research project: A. Conception, B. Organization, C. Execution: Annemarie M.M. Vlaar, Angela Bouwmans and Wim E.J. Weber. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; Annemarie M.M. Vlaar, Angela Bouwmans, and Wim E.J. Weber. Manuscript: A. Writing of the first draft: Annemarie M.M. Vlaar, Angela Bouwmans, B. Review and Critique: Werner H. Mess, Selma C. Tromp and Wim E.J. Weber.

References

1. Litvan I, Agid Y, Jankovic J, Goetz C, Brandel JP, Lai EC, et al. (1996) Accuracy of clinical criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome). Neurology 46(4):922–930
2. Gilman S, Low PA, Quinn N, Albanese A, Ben-Shlomo Y, Fowler CJ, et al. (1999) Consensus statement on the diagnosis of multiple system atrophy. J Neurol Sci 163(1):94–98
3. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55(3): 181–184
4. Bain P, Brin M, Deuschl G, Elble R, Jankovic J, Findley L, et al. (2000) Criteria for the diagnosis of essential tremor. Neurology 54(11 Suppl 4):S7
5. Zijlmans JC, Daniel SE, Hughes AJ, Revesz T, Lees AJ (2004) Clinicopathological investigation of vascular parkinsonism, including clinical criteria for diagnosis. Mov Disord 19(6): 630–640
6. Watanabe H, Saito Y, Terao S, Ando T, Kachi T, Mukai E, et al. (2002) Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. Brain 125(Pt 5):1070–1083
7. Rajput AH, Rozdilsky B, Rajput A (1991) Accuracy of clinical diagnosis in parkinsonism – a prospective study. Can J Neurol Sci 18(3):275–278
8. Dujardin K, Duhamel A, Becquet E, Grunberg C, Defebvre L, Destee A (1999) Neuropsychological abnormalities in first degree relatives of patients with familial Parkinson's disease. J Neurol Neurosurg Psychiatry 67(3): 323–328
9. Ponsen MM, Stoffers D, Booij J, van Eck-Smit BLF, Wolters EC, Berendse HW (2004) Idiopathic hyposmia as a preclinical sign of Parkinson's disease. Ann Neurol 56:173–181
10. Storch A, Hofer A, Kruger R, Schulz JB, Winkler J, Gerlach M (2004) New developments in diagnosis and treatment of Parkinson's disease – from basic science to clinical applications. J Neurol 251(Suppl 6):VI/33–8
11. Lee PH, Yeo SH, Kim HJ, Youm HY (2006) Correlation between cardiac 123I-MIBG and odor identification in patients with Parkinson's disease and multiple system atrophy. Mov Disord 21(11):1975–1977
12. Spiegel J, Mollers MO, Jost WH, Fuss G, Samnick S, Dillmann U, et al. (2005) FP-CIT and MIBG scintigraphy in early Parkinson's disease. Mov Disord 20(5):552–561
13. Vlaar AM, van Kroonenburgh MJ, Kessels AG, Weber WE (2007) Meta-analysis of the literature on diagnostic accuracy of SPECT in parkinsonian syndromes. BMC Neurol 7:27
14. Becker G, Seufert J, Bogdahn U, Reichmann H, Reiners K (1995) Degeneration of substantia nigra in chronic Parkinson's disease visualized by transcranial color-coded real-time sonography. Neurology 45(1):182–184

15. Walter U, Niehaus L, Probst T, Benecke R, Meyer BU, Dressler D (2003) Brain parenchyma sonography discriminates Parkinson's disease and atypical parkinsonian syndromes. Neurology 60(1):74–77
16. Berg D, Siefker C, Becker G (2001) Echogenicity of the substantia nigra in Parkinson's disease and its relation to clinical findings. J Neurol 248(8): 684–689
17. Berg D, Roggendorf W, Schroder U, Klein R, Tatschner T, Benz P, et al. (2002) Echogenicity of the substantia nigra: association with increased iron content and marker for susceptibility to nigrostriatal injury. Arch Neurol 59(6):999–1005
18. Berg D, Becker G, Zeiler B, Tucha O, Hofmann E, Preier M, et al. (1999) Vulnerability of the nigrostriatal system as detected by transcranial ultrasound. Neurology 53(5): 1026–1031
19. Berg D (2007) Disturbance of iron metabolism as a contributing factor to SN hyperechogenicity in Parkinson's disease: implications for idiopathic and monogenetic forms. Neurochem Res 32(10):1646–1654
20. Walter U, Behnke S, Eyding J, Niehaus L, Postert T, Seidel G, et al. (2007) Transcranial brain parenchyma sonogrpahy in movement disorders: state of the art. Ultrasound Med Biol 33(1):15–25
21. Hennerici MG, Meairs SP (2001) Cerebrovascular Ultrasound: Theory, Practice and Future Developments. First edition ed. Cambridge, U.K.: Cambridge University Press
22. Schoning M, Grunert D, Stier B (1989) Transcranial duplex sonography through intact bone: a new diagnostic procedure. Ultraschall Med 10(2): 66–71
23. Walter U, Behnke S, Eyding J, Niehaus L, Postert T, Seidel G, et al. (2007) Transcranial brain parenchyma sonography in movement disorders: state of the art. Ultrasound Med Biol 33(1): 15–25
24. Walter U, Wittstock M, Benecke R, Dressler D (2002) Substantia nigra echogenicity is normal in non-extrapyramidal cerebral disorders but increased in Parkinson's disease. J Neural Transm 109(2):191–196
25. Behnke S, Berg D, Naumann M, Becker G (2005) Differentiation of Parkinson's disease and atypical parkinsonian syndromes by transcranial ultrasound. J Neurol Neurosurg Psychiatry 76(3): 423–425
26. Becker G, Becker T, Struck M, Lindner A, Burzer K, Retz W, et al. (1995) Reduced echogenicity of brainstem raphe specific to unipolar depression: a transcranial color-coded real-time sonography study. Biol Psychiatry 38(3):180–184
27. Glaser M, Weber U, Hinrichs H, Niehaus L (2006) Neuroimaging of midbrain structures with different phased array ultrasound systems. Klin Neurophysiol 37:165–168
28. Budisic M, Trkanjec Z, Bosnjak J, Lovrencic-Huzjan A, Vukovic V, Demarin V (2009) Distinguishing Parkinson's disease and essential tremor with transcranial sonography. Acta Neurol Scand 119(1):17–21
29. Schweitzer KJ, Hilker R, Walter U, Burghaus L, Berg D (2006) Substantia nigra hyperechogenicity as a marker of predisposition and slower progression in Parkinson's disease. Mov Disord 21(1):94–98
30. Huang YW, Jeng JS, Tsai CF, Chen LL, Wu RM (2007) Transcranial imaging of substantia nigra hyperechogenicity in a Taiwanese cohort of Parkinson's disease. Mov Disord 22(4):550–555
31. Godau J, Schweitzer KJ, Liepelt I, Gerloff C, Berg D (2007) Substantia nigra hypoechogenicity: definition and findings in restless legs syndrome. Mov Disord 22(2):187–192
32. Godau J, Wevers AK, Gaenslen A, Di Santo A, Liepelt I, Gasser T, et al. (2008) Sonographic abnormalities of brainstem structures in restless legs syndrome. Sleep Med 9(7):782–789
33. Kim JY, Kim ST, Jeon SH, Lee WY (2007) Midbrain transcranial sonography in Korean patients with Parkinson's disease. Mov Disord 22(13): 1922–1926
34. Walter U, Dressler D, Wolters A, Wittstock M, Greim B, Benecke R (2006) Sonographic discrimination of dementia with Lewy bodies and Parkinson's disease with dementia. J Neurol 253(4):448–454
35. Tromp SC, Vlaar AMM, Kroonenburgh MJPG, Mess WH, Nijs de T, Winogrodzka A, et al. (2007)The diagnostic value of transcranial duplex scanning and SPECT imaging versus clinical diagnosis (clinical prospective study). Movement Disorders 22(Suppl 16): S220
36. Tsai CF, Wu RM, Huang YW, Chen LL, Yip PK, Jeng JS (2007) Transcranial color-coded sonography helps differentiation between idiopathic Parkinson's disease and vascular parkinsonism. J Neurol 254(4):501–507
37. Stockner H, Seppi K, Kiechl S, Schmidauer C, Sojer M, Schwaiger M, et al. (2006) Midbrain transcranial sonography finding in a population based study. Movement Disorders 21(Suppl 15):S634
38. Okawa M, Miwa H, Kajimoto Y, Hama K, Morita S, Nakanishi I, et al. (2007) Transcranial sonography of the substantia nigra in Japanese patients with Parkinson's disease or atypical parkinsonism: clinical potential and limitations. Intern Med 46(18):1527–1531
39. Walter U, Dressler D, Wolters A, Probst T, Grossmann A, Benecke R (2004) Sonographic discrimination of corticobasal degeneration vs progressive supranuclear palsy. Neurology 63(3): 504–509
40. Walter U, Dressler D, Probst T, Wolters A, Abu-Mugheisib M, Wittstock M, et al. (2007) Transcranial brain sonography findings in discriminating between parkinsonism and idiopathic Parkinson disease. Arch Neurol 64(11): 1635–1640
41. Berg D, Siefker C, Ruprecht-Dorfler P, Becker G (2001) Relationship of substantia nigra echogenicity and motor function in elderly subjects. Neurology 56(1):13–17
42. Ruprecht-Dorfler P, Berg D, Tucha O, Benz P, Meier-Meitinger M, Alders GL, et al. (2003) Echogenicity of the substantia nigra in relatives of patients with sporadic Parkinson's disease. Neuroimage 18(2):416–422
43. Walter U, Klein C, Hilker R, Benecke R, Pramstaller PP, Dressler D (2004) Brain parenchyma sonography detects preclinical parkinsonism. Mov Disord 19(12):1445–1449
44. Sommer U, Hummel T, Cormann K, Mueller A, Frasnelli J, Kropp J, et al. (2004) Detection of presymptomatic Parkinson's disease: combining smell tests, transcranial sonography, and SPECT. Mov Disord 19(10):1196–202
45. Shahed J, Jankovic J (2007) Exploring the relationship between essential tremor and Parkinson's disease. Parkinsonism Relat Disord 13:67–76
46. Walter U, Hoeppner J, Prudente-Morrissey L, Horowski S, Herpertz SC, Benecke R (2007) Parkinson's disease-like midbrain sonography abnormalities are frequent in depressive disorders. Brain 130(7):1799–807
47. Walter U, Dressler D, Wolters A, Wittstock M, Benecke R (2007) Transcranial brain sonography findings in clinical subgroups of idiopathic Parkinson's disease. Mov Disord 22(1): 48–54

48. Becker T, Becker G, Seufert J, Hofmann E, Lange KW, Naumann M, et al. (1997) Parkinson's disease and depression: evidence for an alteration of the basal limbic system detected by transcranial sonography. J Neurol Neurosurg Psychiatry 63(5):590–596
49. Spiegel J, Hellwig D, Mollers MO, Behnke S, Jost W, Fassbender K, et al. (2006) Transcranial sonography and [123I]FP-CIT SPECT disclose complementary aspects of Parkinson's disease. Brain 129(Pt 5):1188–1193
50. Doepp F, Plotkin M, Siegel L, Kivi A, Gruber D, Lobsien E, et al. (2008) Brain parenchyma sonography and 123I-FP-CIT SPECT in Parkinson's disease and essential tremor. Mov Disord 23(3): 405–410
51. Mijajlovic M, Dragasevic N, Stefanova E, Petrovic I, Svetel M, Kostic VS (2008) Transcranial sonography in spinocerebellar ataxia type 2. J Neurol 255(8): 1164–1167
52. Postert T, Lack B, Kuhn W, Jergas M, Andrich J, Braun B, et al. (1999) Basal ganglia alterations and brain atrophy in Huntington's disease depicted by transcranial real time sonography. J Neurol Neurosurg Psychiatry 67(4): 457–462
53. Prestel J, Schweitzer KJ, Hofer A, Gasser T, Berg D (2006) Predictive value of transcranial sonography in the diagnosis of Parkinson's disease. Mov Disord 21(10):1763–1765
54. Ressner P, Skoloudik D, Hlustik P, Kanovsky P (2007) Hyperechogenicity of the substantia nigra in Parkinson's disease. J Neuroimaging 17(2):164–167
55. Schmidauer C, Sojer M, Seppi K, Stockner H, Hogl B, Biedermann B, et al. (2005) Transcranial ultrasound shows nigral hypoechogenicity in restless legs syndrome. Ann Neurol 58(4): 630–634
56. Schweitzer KJ, Behnke S, Liepelt I, Wolf B, Grosser C, Godau J, et al. (2007) Cross-sectional study discloses a positive family history for Parkinson's disease and male gender as epidemiological risk factors for substantia nigra hyperechogenicity. J Neural Transm 114(9):1167–1171
57. Stockner H, Sojer M, Seppi K, Mueller J, Wenning GK, Schmidauer C, et al. (2007) Midbrain sonography in patients with essential tremor. Mov Disord 22(3):414–417
58. Gaenslen A, Unmuth B, Godau J, Liepelt I, Di Santo A, Schweitzer KJ, et al. (2008) The specificity and sensitivity of transcranial ultrasound in the differential diagnosis of Parkinson's disease: a prospective blinded study. Lancet Neurol 7(5):417–424
59. Becker G, Struck M, Bogdahn U, Becker T (1994) Echogenicity of the brainstem raphe in patients with major depression. Psychiatry Res 55(2):75–84
60. Berg D, Supprian T, Hofmann E, Zeiler B, Jager A, Lange KW, et al. (1999) Depression in Parkinson's disease: brainstem midline alteration on transcranial sonography and magnetic resonance imaging. J Neurol 246(12): 1186–1193
61. Doepp F, Plotkin M, Siegel L, Kivi A, Gruber D, Lobsien E, et al. (2008) Brain parenchyma sonography and (123)I-FP-CIT SPECT in Parkinson's disease and essential tremor. Mov Disord 23(3):405–410