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Ultrasound Application in Movement Disorders

인제대학교 의과대학 신경과학교실

백 종 삼

Transcranial Sonography (TCS)

- Imaging of intracranial structures (brain parenchyma) in B-mode
- Without imaging of intracranial arteries
- Using high-resolution systems

Equipment of TCS

Through **preauricular acoustic bone window**, a single expert for TCS examined the echogenicity of substantia nigra using **2-5MHz** sonographic device with **depth of 16 cm** and a **dynamic range of 45 dB**.

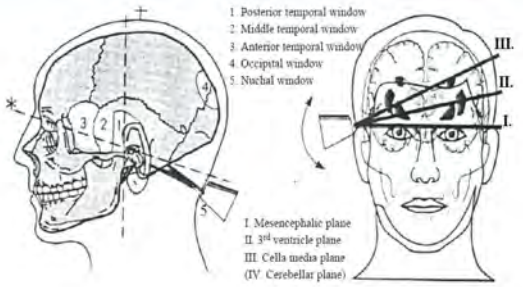
TCS system settings

	High-end system*
Transducer	2-0-3.5 MHz
Penetration depth	14-16 cm
Dynamic range	45-55 dB
Contour amplification	Medium to high
Image brightness	Adapt as needed
Time gain compensation	Adapt as needed
Post-processing parameters	Moderate suppression of low echogenic signals

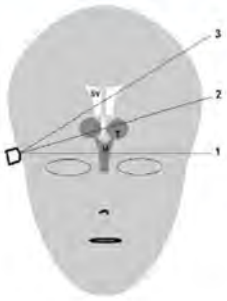
*Any high-end ultrasound machine that is also suitable for transcranial vascular sonography can be used. In papers published up to March 2008, the ultrasound systems of the following manufacturers have been applied: Advanced Technology Laboratories (Washington, USA) systems Ultramark-2000 and Ultramark-5;[10] General Electric (Milwaukee, WI, USA) system Logiq 7;[4,6] Philips (Eindhoven, the Netherlands) systems HDI 5000,[4,5] SONOS 4500,[8,9,14] and SONOS 5500;[2,3] Siemens (Erlangen, Germany) systems Sonoline CT,[7,9,11] Sonoline Elegra,[2,9,13] and Acuson Aritaro;[4] and Toshiba (Tokyo, Japan) systems SSH-140A,[4] and Aplio.[4]

Table 1: TCS system settings

Transcranial Sonography (TCS)

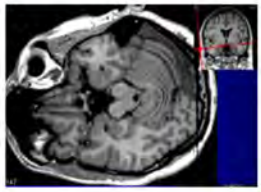


TCS : Standardized Investigation



- **3) Cella media plane:**
  - Lateral ventricle (Cella media)
- **2) Thalamic plane:**
  - Thalamus
  - Leniform nucleus
  - Caudate nucleus
  - 3rd Ventricle
  - Lateral Ventricle/anterior horn
- **1) Mesencephalic plane:**
  - Substantia nigra
  - Nucleus ruber
  - Raphe

Sonographic anatomy of the brainstem



Diagnostic Fields

- Brain tumors
- Intracerebral hematomas
- Vascular malformations
- Hydrocephalus
- Neurodegenerative disorders (Parkinson's disease, idiopathic dystonia, Huntington's disease...)

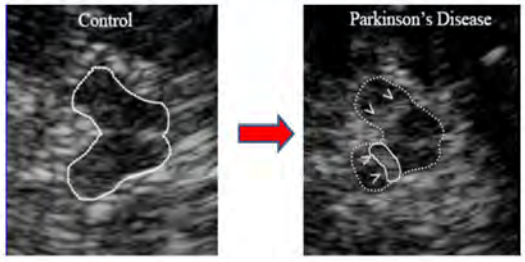
Why TCS in Movement Disorders?

- Non-invasive
- No movement artifacts
- Detects changes not visible on MRI or CT
- High image resolution of small echogenic deep brain structures – better than MRI under clinical conditions

But···

- A quality of a bone window (thickness of skull, homogeneity, structure-osteoporosis) : 80-90%
- Dependent on sonographer skill and experience
- Hardware and software of sonographic devices

Echogenicity of the Substantia Nigra



Evaluation of Substantia Nigra

- **Area of echogenic substantia nigra**

  Normal ≤0.19 cm^2

  border zone = 0.2-0.24 cm^2

  pathologic ≥ 0.25 cm^2

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Midbrain Transcranial Sonography in Korean Patients with Parkinson's Disease

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Abstract: Transcranial sonography (TCS) is potentially useful for the diagnosis of Parkinson's disease (PD). However, studies on TCS have so far been restricted to European populations. To investigate the efficacy of TCS in Korean PD patients and its correlation with the clinical features, we carried out midbrain TCS in 43 PD patients and 35 normal controls and evaluated the area of the substantia nigra (SN) hyperechogenicity and its ratio to the area of the whole midbrain. In 16 subjects (21%), TCS was unsuccessful due to insufficient acoustic temporal bone windows. The mean area of bilateral SN hyperechogenicity and its ratio to the midbrain area were greater in the PD patients than that in the controls ($P < 0.01$). In the PD patients, the area of SN hyperechogenicity and its ratio to the individual midbrain area were moderately correlated with the PD duration ($r = 0.526$ and 0.536, $P = 0.01$, respectively) but not with the age, UPDRS motor scores or H-Y stage. There was no difference in the SN hyperechogenicity between the tremor-dominant, akinetic-rigid, and mixed-type PD patients. In conclusion, midbrain TCS is an effective diagnostic tool for detecting PD in the Korean population. However, it does not reflect the severity or phenotypes of parkinsonism. © 2007 Movement Disorder Society

Key words: transcranial sonography; substantia nigra; Parkinson's disease; Korean

Echogenicity of the SN in PD

- 3 Studies
  1) Becker et al., 1995
  2) Berg et al., 2001
  3) Walter et al., 2002
- Comprising 172 patients
- ***Prevalence > 90%***

Brain parenchyma sonography discriminates Parkinson's disease and atypical parkinsonian syndromes

Table 1 Demographic data of patients studied

Data	IPD patients	MSA patients	PSP patients
No.	25	16	9
Sex	11 men; 14 women	5 men; 11 women	5 women; 4 men
Age, y			
Mean ± SD	67.7 ± 6.8	66.0 ± 9.8	71.6 ± 5.7
Range	56–84	48–79	61–80
Disease duration, y			
Mean ± SD	3.7 ± 3.1	3.7 ± 1.9	4.8 ± 1.7
Range	1–10	2–8	3–8
UPDRS-III score, mean ± SD	28.7 ± 14.3	36.3 ± 16.6	66.5 ± 19.0

IPD = idiopathic PD; MSA = multiple-system atrophy; PSP = progressive supranuclear palsy; UPDRS-III = Unified Parkinson's Disease Rating Scale, motor part.

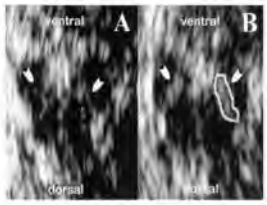


Figure 1. Sonographic images of identical midbrain axial sections in two patients. The butterfly-shaped midbrain section of low echogenicity is surrounded by the hyperechogenic basal cisterns. (A) Patient with atypical parkinsonism syndrome (multiple-system atrophy) exhibiting normal, nearly invisible substantia nigra (thick arrowheads; thin arrowheads = red nuclei). (B) Patient with idiopathic PD. Note the marked bilateral hyperechogenicity of the substantia nigra (arrowheads). Echogenic area of the left substantia nigra was encircled for computerized measurement.

Table 2 Qualitative assessment of brain parenchyma echogenicity of substantia nigra, thalamus, lenticular nucleus, and caudate nucleus in patients with idiopathic PD and atypical parkinsonian syndromes

Structure	Brain parenchyma echogenicity		
	Group IPD, n = 25	Group APS, n = 25, assessable n = 23	Significance[a]
Substantia nigra	Normal: 1; hyperechogenicity*: 24; moderate: 5 (ul: 3; bl: 2); marked: 19 (ul: 13; bl: 6)	Normal: 21; hyperechogenicity*: 2; moderate 2 (ul: 0; bl: 2); marked: 0 (ul: 0; bl: 0)	$p < 0.001$
Thalamus	Normal: 25; hyperechogenicity*: 0	Normal: 23; hyperechogenicity*: 0	
Lenticular nucleus[†]	Normal: 17; hyperechogenicity*: 5	Normal: 5; hyperechogenicity*: 17	$p < 0.001$
Caudate nucleus[†]	Normal: 7; hyperechogenicity*: 13	Normal: 8; hyperechogenicity*: 14	$p > 0.3$

Classifications were based on the most affected side. * Hyperechogenicity was determined by substantia nigra size. * Hyperechogenicity was determined by structure visibility (see Methods).

[a] Mann–Whitney *U*-test.
[†] Three patients from Group IPD and one patient from Group APS were not evaluated owing to insufficient temporal acoustic bone windows.

IPD = idiopathic PD; APS = atypical parkinsonian syndromes; ul = unilateral; bl = bilateral.

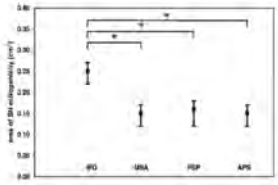


Table 3 Brain parenchyma sonography findings indicating idiopathic PD rather than atypical parkinsonian syndromes

Sonographic findings	Sensitivity, %	PPV, %	Specificity, %	Significance[a] between findings in Groups IPD and APS
SN echogenic area ≥0.25 cm^2	96	92	91	$p < 0.001$
SN echogenic area ≥0.25 cm^2	76	100	100	$p < 0.001$
Lentiform nucleus normoechogenicity	77	77	77	$p < 0.001$
Width of third ventricle <9 mm	74	71	67	$p < 0.05$

[a] Mann–Whitney *U*-test.

PPV = positive predictive value; IPD = idiopathic PD; APS = atypical parkinsonian syndromes; SN = substantia nigra.

Differentiation of Parkinson's disease and atypical parkinsonian syndromes by transcranial ultrasound

S Behnke, D Berg, M Naumann, G Becker

J Neurol Neurosurg Psychiatry 2005;76:423–425. doi: 10.1136/jnnp.2004.049221

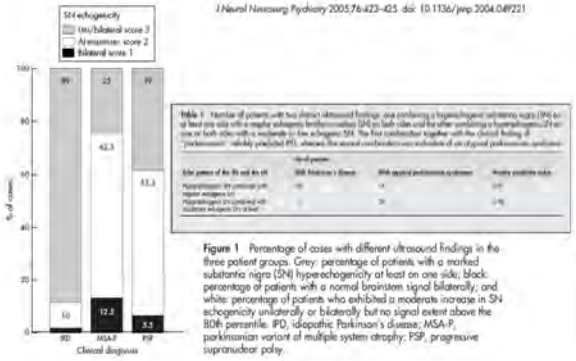


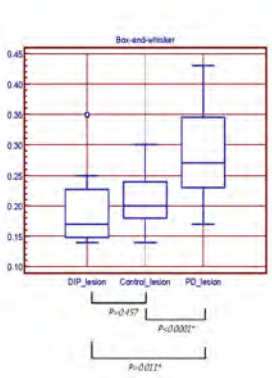
Figure 1 Percentage of cases with different ultrasound findings in the three patient groups. Grey: percentage of patients with a marked substantia nigra (SN) hyperechogenicity of least on one side; black: percentage of patients with a normal brainstem signal bilaterally; and white: percentage of patients who exhibited a moderate increase in SN echogenicity unilaterally or bilaterally but no signal extent above the 90th percentile. IPD, idiopathic Parkinson's disease; MSA-P, parkinsonian variant of multiple system atrophy; PSP, progressive supranuclear palsy.

TCS finding	Indicated condition	Excluded condition	Sensitivity†	Specificity†	PPV†
Hyperechogenicity of the substantia nigra*	PD	MSA-P or PSP	82-98 (92)	70-100 (86)	84-100 (91)
Normal substantia nigra*	MSA-P or PSP	PD	72	98	93-95
Normal substantia nigra plus hyperechogenicity of the lenticular nucleus*	MSA-P or PSP	PD	56-59	99-100	96-100
Normal substantia nigra plus hyperechogenicity of the lenticular nucleus*	MSA-P	PD	65	100	100
3V (>10 mm) plus hyperechogenicity of the lenticular nucleus*	PSP	PD	84	98	94

3V=width of third ventricle (minimally measured width); PPV=positive predictive value; *vs. parkinsonian type of MSA-P and PSP. †percent. ‡result of pooled analysis of all five studies that included 500 patients with adequate assessability on TCS, of whom 353 had definite PD, 86 had probable or possible MSA-P, and 61 had probable or possible PSP.

Table 2: Sensitivity and specificity of TCS findings to discriminate between idiopathic PD and atypical PS*

Drug Induce PD vs. IPD



DIP

IPD

In Healthy Subjects ?

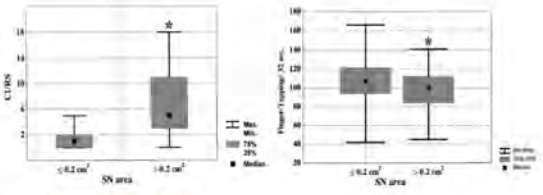
- 417 healthy controls
  (20-80 years, median: 38.1 years)

➔ About 8-10% of healthy adults display increased echogenicity similar to Parkinson's disease

➔ *Is there any relevance of the ultrasound marker increased SN-echogenicity in healthy people?*

Relationship of substantia nigra echogenicity and motor function in elderly subjects

Daniela Berg, MD; Christiane Siefker; Petra Ruprecht-Dörfler, MD; and Georg Becker, MD



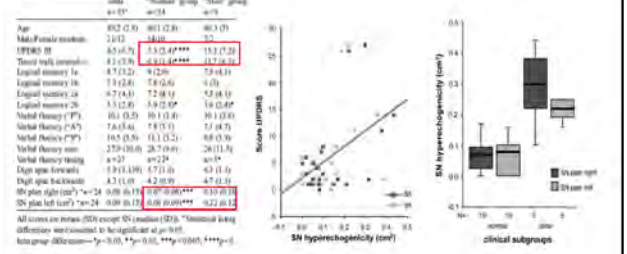
More severe motor deficit

Total: 79, Hypo: 58, Hyper: 21

Substantia nigra echomorphology in the healthy very old: Correlation with motor slowing

NeuroImage

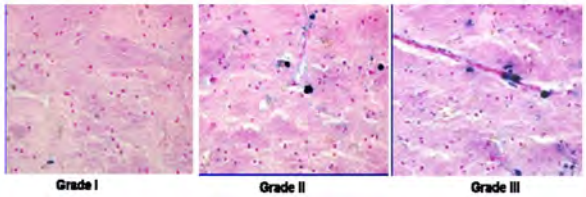
S. Behnke,[a,*] K.L. Double,[b] S. Duma,[b] G.A. Broe,[b] V. Guenther,[a] G. Becker,[a] and G.M. Halliday[b]



Causes of increased SN echogenicity

- Iron metabolism
- Structural changes of brain cells
  - apoptosis and neuronal loss in SN
  - morphological changes of neurons

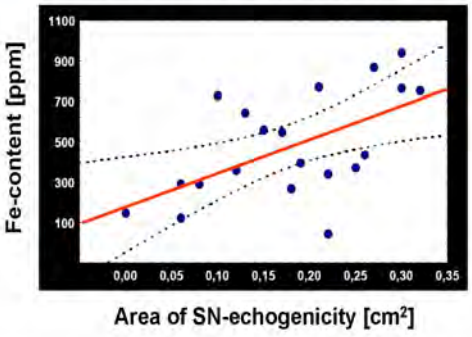
Semiquantitative Assessment



Grade	Number	Iron contents [μg/mg wet tissue]	Echogenicity [cm²]
I	42	0.15±0.07	0.17±0.08
II	13	0.17±0.05	0.24±0.09
III	5	0.26±0.07	0.25±0.05

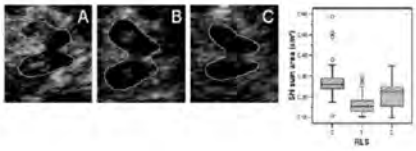
Biochemical Investigations

Spearman's rank correlation; r=0.57; p=0.007



In Restless legs syndrome ?

Substantia Nigra Hypoechogenicity: Definition and Findings in Restless Legs Syndrome



RLS and PD

- Exploring the relationship between RLS and PD
  - dopaminergic dysfunction
  - response to dopaminergic agents
  - ➔ *may share common pathophysiology*
- The frequency of RLS in PD
  : estimated as ranging from 7.9% to 20.8%
  : *16.3% in Korean Study*

Parkinsonism and Related Disorders

Short communication

Sonographic abnormalities in idiopathic restless legs syndrome (RLS) and RLS in Parkinson's disease

Jung Ho Ryu, Myung Sik Lee, Jong Sam Baik

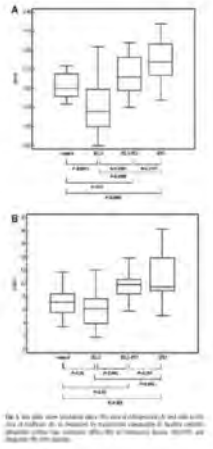
ARTICLE INFO

ABSTRACT

Table 1
Demographic data and SN echogenicity of patients with iRLS, RLS-PD, IPD and normal controls.

	Controls	iRLS	RLS-PD	IPD
Patients, n	35	41	19	25
Gender (male/female)	2.5	0.78	1.11	0.67
Age, Mean ± SD	60.1 ± 11.3	62.3 ± 15.5	71.3 ± 7.8	68.5 ± 11.3
PLMS, n (%)		7 (17.1)	2 (10.5)	
SN echogenicity (cm^2), Mean ± SD	0.21 ± 0.03	0.15 ± 0.06	0.24 ± 0.05	0.27 ± 0.07
SN echogenicity ratio,[a] Mean ± SD	7.3 ± 2.0	6.2 ± 2.6	9.9 ± 2.2	10.9 ± 3.4
SN area ≤0.20 cm^2 on one side (%)	31.4	74.2	26.7	15.8
Poor temporal window (%)	0	24.4	21.1	24

PLMS, Periodic Limb Movements in Sleep; SN, Substantia Nigra.
[a] Unilateral SN hyperechogenic area/half midbrain area ratio.



In Essential Tremor ?

Movement Disorders Vol. 22, No. 7, 2007

Midbrain Sonography in Patients with Essential Tremor

Heike Stockner, MD, Martin Sojer, MD, Klaus Seppi K, MD, Joerg Mueller, MD, Gregor K. Wenning, MD, Christoph Schmidauer, MD, and Werner Poewe, MD*

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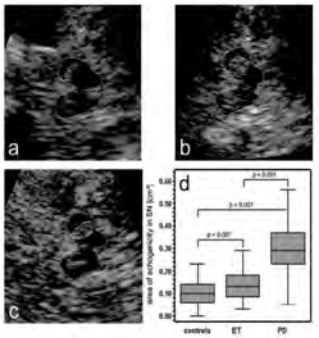
TABLE 1. *Demographic data and SN echogenicity of patients with ET and PD and normal controls*

	Control subjects	ET patients	PD patients
Patients, n	100	44	100
Female	50	20	35
Male	50	24	65
Age			
Mean ± SD	64.2 ± 8.7	69.2 ± 10.8	65.2 ± 8.6
Age of onset			
Mean ± SD	–	46.1 ± 19.3	59.9 ± 10.2
Disease duration			
Mean ± SD	–	19.4 ± 16.3	9.27 ± 6.8
SN echogenicity (cm^2)			
Mean ± SD	0.11 ± 0.065	0.34 ± 0.084	0.30 ± 0.102
Hyperechogenicity (%)	3	16	75

ET = Essential Tremor, PD = Parkinson's disease, SN = Substantia nigra, SD = Standard deviation.



Raphe Echogenicity Assessment

- Semiquantitiative

Grade I: not visible,
isoechogenic to adjacent hypoechogenic brainstem or interrupted
Grade II: hyperechogenic, comparable with red nucleus or basal cisterns, not interrupted

or

Grade I: not visible
Grade II: slightly echogenic, interrupted
Grade III: normal (red nucleus as reference)

➔ ***Important: Scanning from both sides, the best signal counts!!***

Raphe and Depression

- Unipolar depression
  60 pts vs 60 controls (Becker et al. 1994, 1995)
  > 73% of patients displayed reduced echogenicity
  > normal echogenicity in all controls
- Parkinson's disease and depression
  33 depressive vs 28 non-depressive PD patients (Becker et al. 1997)
  > markedly reduced echogenicity in 58% of depressive PD vs. 7% of non-depressive PD
- Depression in Huntington's disease (Poster et al. 1999)
- Wilson's disease and depression (Walter et al. 2005)
- MS and depression
  31 depressive vs. 47 non-depressive MS-patients
  > no significant difference between the groups

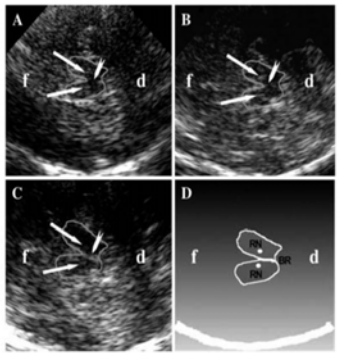


Fig. 1. Transcranial sonography (TCS) axial scans of the midbrain in three patients with depressive states. The midbrain is surrounded for better recognition. f = frontal, d = dorsal. A) Midbrain TCS image of a patient with markedly reduced brainstem raphe echogenicity (score 1). The brainstem raphe (arrow head) is not depicted, although the red nuclei (arrows) are clearly visible. B) Midbrain TCS image of a patient with moderately reduced brainstem raphe echogenicity (score 2). The brainstem raphe (arrow head) is weakly echogenic and interrupted, although the red nuclei (arrows) are clearly visible. C) Midbrain TCS image of a patient with normal brainstem raphe echogenicity (score 3). The brainstem raphe (arrow head) is depicted as a highly echogenic midline structure with echogenicity similar to the red nuclei (arrows) and the highly echogenic basal cisterns. D) Schematic illustration of (C). BR = brainstem raphe, RN = red nucleus.

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Mesencephalic midline change on transcranial sonography in early Parkinson's disease patients with depression

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ABSTRACT

Recently, several studies using transcranial sonography (TCS) have resulted in the alteration of the mesencephalic midline in patients with depression. We aimed to investigate and compare sonographic abnormalities in the brainstem raphe (BR) in patients with Parkinson's disease (PD) and controls, according to presence of depression. Study participants totaled 61 patients with PD (29 PD without depression, 32 PD with depression) and 41 controls. Results indicated that decreased BR echogenicity was much higher in PD patients with depression (PD+D) than in those without depression (PD−D). Of the 61 PD patients, 32 (52.4%) had depression as diagnosed by psychiatric assessment, and 13 (17.6%) were excluded, due to insufficient temporal windows. Based on these results, the use of TCS with respect to the mesencephalic midline may be useful in detecting depression, a risk factor for the development of PD.

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Table 1
Demographic data of patients with Parkinson's disease with depression (PD+D), without depression (PD−D), and controls.

	Control-D	PD−D	PD+D	p value
Number of patients	41	29	32	
Age (mean ± SD)	57.9 ± 12.6	68.6 ± 7.3	67.7 ± 7.3	0.632
Age (range, years)	34-84	54-83	51-79	
Gender (male/female)	28/13	16/13	22/10	0.397
H-Y stage (mean ± SD)		1.1 ± 0.2	1.4 ± 0.7	0.029
Type (tremor/akinetic)		19/10	12/20	0.053
Previous depression Hx. (%)	0	0	6 (18.8)	

H-Y, Hoehn and Yahr.

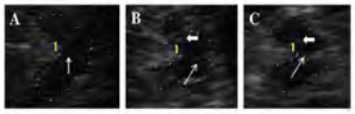

Fig. 1. Sonographic images of corresponding midbrain axial sections in three subjects. The butterfly-shaped midbrain was encircled for better visualization. Thick arrows indicate red nuclei; thin arrow, brainstem raphe (BR). (A) Subject without visible BR (Grade I), (B) Subject with slightly echogenic/interrupted BR (Grade II), (C) Subject with normal BR echogenicity (Grade III).

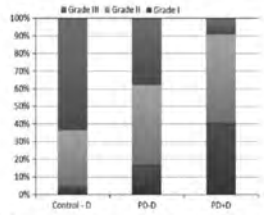

Fig. 2. Diagram showing the degree of brainstem raphe (BR) echogenicity in patients with Parkinson's disease with depression (PD+P), those without depression (PD−D), and controls (Grade I = BR not visible, Grade II = slightly echogenic/interrupted BR, Grade III = normal BR echogenicity).

Table 2
Demographic data and clinical scores at the time of transcranial sonography of patients with normal and abnormal echogenicity of brainstem raphe (BR).

	BR normal	BR hyperechogenic	p value
Number of patients	16	45	
Gender (male/female)	10/6	28/17	0.76
Age (mean ± SD)	65.4 ± 6.2	68.2 ± 7.3	0.068
H-Y stage (mean ± SD)	1.11 ± 0.21	1.29 ± 0.49	0.174
Type (tremor/akinetic)	9/7	22/23	0.849
BDI score	14.2 ± 8.7	17.6 ± 8.5	0.304
HAM-D score	3.6 ± 2.6	13.8 ± 8.3	0.007

H-Y, Hoehn and Yahr; BDI, Beck Depression Inventory; HAM-D, Hamilton depression scale.

TCS and Depression

- TCS provides a unique opportunity to image the raphe

Advantages: easily applicable
rapidly performable (dyskinetic, agitated patients)
low costs

Disadvantages: dependent on investigator
insufficient bone windows in about 10%

Helpful in different diagnosis of
- depression
- early PD
- PD with depression

In Dementia ?

- There is no basal ganglia TCS finding specific for dementia or dementia in PD
- Dilatation of 3rd ventricle and of frontal horns is a consistent TCS finding in dementia disorders
- TCS findings related to non-motor features in PD are:
  - Midbrain raphe hypoechogenicity (Depression, urge incontinence)
  - Caudate nucleus hyperechogenicity (Drug-induced psychosis)
  - Frontal horn dilatation (Dementia)

Future

- Large prospective blinded studies
- Evaluation of both sonographic parameters
- Using a computer automatic measurements (blinded sonographer)
- Is TCS useful not only in differentiation between healthy subjects and PD patients but also in differentiation between several movement disorders (PD, MSA, PSP..)

Take Home Messages

- **TCS is useful tools**
  - in the early diagnosis of PD
  - in the differential diagnosis vs. atypical Parkinsonian SD, tremor, sporadic Parkinsonian SD
  - in detection of a subclinical impairment
  - to evaluate pathophysiologic processes in PD
  - to identify subgroups of the disorder
- **Limitations**
  - poor window
  - validation