TRANSCRANIAL SONOGRAPHY IN MOVEMENT DISORDERS

Petra Bartováa, David Skoloudíka,c, Michal Bara, Pavel Ressnerb, Petr Hlustíkc, Roman Herzígc, Petr Kanovskyc

a Department of Neurology, University Hospital, Ostrava, Czech Republic
b Department of Neurology, Hospital Nový Jičín, Czech Republic
c Department of Neurology, University Hospital and Medical School Olomouc, Czech Republic
e-mail: petrabartova@seznam.cz

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Background: Transcranial sonography (TCS) in the B-mode has the ability to image, infratentorial and supratentorial brain structures. For this reason, it has potential use in the diagnosis and differential diagnosis of various intracranial pathologies.

Methods and Results: The authors reviewed the contribution of TCS to the differentiation of a number of neurodegenerative diseases: in parkinsonian syndromes, TCS can evaluate echogenicity changes in specific structures such as the hyperechogenic area of the substantia nigra (SN) in Parkinson’s disease and the hyperechogenic caudate nucleus in Huntington’s disease as well as the hyperechogenic lentiform nucleus (LN) in dystonia and Wilson’s disease. In parkinson-plus syndromes, TCS may detect changes in width of the third ventricle and of the frontal horns of the lateral ventricle. The hyperechogenic SN can also be used in healthy populations as a marker of subclinical injury to the nigrostriatal system.

Conclusion: TCS is a quick, safe and non-invasive method. It could be helpful in differentiation between several movement disorders together with clinical examination and other neuroimaging methods.

INTRODUCTION

The differentiation between idiopathic Parkinson’s disease (PD) and atypical parkinsonian syndromes can be difficult especially at the beginning of the disease. A diagnosis of PD is based on clinical symptoms (UK Brain Bank criteria) and response to L-DOPA treatment1. Available neuroimaging methods such as computer tomography (CT) and magnetic resonance (MR) may detect structural abnormalities of the brain and contribute to differential diagnosis of parkinsonian syndromes. However, they often report normal findings, especially in the early stages of the disease. Moreover, the severity of the disease lacks an imaging correlate1.

Other neuroimaging methods such as single photon emission tomography (SPECT) and positron emission tomography (PET) identify biochemical changes in the nigrostriatal system and may detect a decrease in dopaminergic cells in the SN14. However, these techniques are very expensive and not widely accessible.

Transcranial sonography evaluation – methods

Transcranial sonography (TCS) on the other hand, is a neuroimaging method with the ability to provide data on various brain structures in its B-mode7,8. In addition, transcranial color-coded duplex sonography is able to provide information on the intracranial arteries and veins as well7,4. It is very quick, safe and non-invasive. The main limitation is that some patients do not have a sufficient bone window7,8. Although TCS resolution is inferior to MR, it can detect mesencephalic nuclei, assess the width of the third ventricle and the frontal horns of lateral ventricles. TCS could help in the differential diagnosis of PD and atypical parkinsonian syndromes (APS) in addition to clinical examination and other paraclinical, neuroimaging and genetic methods7,8.

Transcranial sonography evaluation – methods

TCS evaluation of brain structures is realized through a transcranial (preauricular) acoustic window using transcranial duplex probe with the frequency about 1–4 MHz, dynamic range is 50-170 dB. Penetration depth is 14-16 cm with the imaging of the contralateral bone. TCS allows the depiction of brain structures in detail, e.g., mesencephalon with the zoom (Figure 1). Axial resolution of TCS evaluation is about 0.5-1.0 mm, lateral resolution is about 3.0 mm. The main limitation of TCS evaluation is insufficient transtemporal window, which is missing in 8–20 % of patients, depending on age and sex8,12. There is also a dependency on examiner’s skills7,8,11.

In May 2004, at the 9th Meeting of ESNCH (European Society of Neurosonology and Cerebral Hemodynamics) a standardized procedure for TCS in neurodegenerative diseases was approved as mentioned by Water et al.7.
Table 1. Transcranial Sonography Studies in Parkinsonism

<table>
<thead>
<tr>
<th>Authors</th>
<th>PD Patients</th>
<th>Healthy Controls</th>
<th>APS Patients</th>
<th>UPDRS III (SD)</th>
<th>Se%</th>
<th>Sp%</th>
<th>PPV</th>
<th>NPV</th>
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<tbody>
<tr>
<td>Becker et al. (1995)⁹</td>
<td>30</td>
<td>30</td>
<td>-</td>
<td>27.7 (13.1)†</td>
<td>40</td>
<td>100</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Walter et al. (2002)¹¹</td>
<td>30</td>
<td>30</td>
<td>-</td>
<td>35.7 (19.7)</td>
<td>100</td>
<td>88</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Ruprecht et al. (2003)²²</td>
<td>14</td>
<td>582</td>
<td>-</td>
<td>-</td>
<td>92</td>
<td>55.10</td>
<td>0.33</td>
<td>0.97</td>
</tr>
<tr>
<td>Walter et al. (2004)³⁸</td>
<td>7</td>
<td>73</td>
<td>-</td>
<td>39.1 (20.5)</td>
<td>100</td>
<td>28.50</td>
<td>0.58</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Studies comparing PD to APS

| Walter et al. (2003)³⁶ | 25          | -                | 16 MSA 9 PSP | 28.7 (14.5)    | 91    | 96    | -    | -   |
| Behnke et al. (2005)³⁵ | 102         | -                | 34 MSA 21 PSP | 56.5 (19)*  | 0.964 | 0.95  | -    | -   |

Studies comparing PSP and CBD

| Walter et al. (2004)³⁹ | -           | -                | 13 PSP 8 CBD | 43.5 (20.1)*  | 88    | 100   | -    | -   |

Studies within the PD-group, without controls

| Berg et al. (2001)¹⁰ | 112         | -                | -            | 16†           | 91    | -     | -    | -   |
| Berg et al. (2005)¹⁹ | 16          | -                | -            | 16 (10) 26 (10) # | 81    | -     | -    | -   |

Footnotes

† = Columbia University Rating Scale (SD), * = severity of APS, # = at five years follow up, – – not stated, not applicable

Table 2. Evaluation of echogenicity of substantia nigra using transcranial sonography

<table>
<thead>
<tr>
<th>Echogenicity</th>
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<tr>
<td>Grade I</td>
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<tr>
<td>Grade II</td>
</tr>
<tr>
<td>Grade III</td>
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<tr>
<td>Grade IV</td>
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<td>Grade V</td>
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</table>

TCS evaluation substantia nigra in Parkinson’s disease

In patients with PD, TCS is able to detect a hyper-echogenic and enlarged area of the SN as a marker of striatonigral damage. It has a sensitivity of about 90 % and specificity of about 90 % (ref.¹⁴–¹⁸) – see Table 1.

The first evaluations of the substantia nigra in PD patients were published in 1995. Becker et al. described SN in idiopathic PD as an echogenic nucleus inside the anechogenic butterfly mesencephalon (Fig. 2) through the transtemporal window. They assessed⁹ the area of the hyperechogenic SN nucleus and set up a threshold for pathological area of SN at ≥0.19 cm².

The following study of Walter et al. estimated the upper limit of the normal area of the hyperechogenic SN
Transcranial sonography in movement disorders

Fig. 1. Transcranial sonography: mesencephalon with normal finding of substantia nigra – Grade II.
1 – Mesencephalon, 2 – Fourth ventricle, 3 – Substantia nigra

Fig. 2. Transcranial sonography: hyperechogenic enlarged substantia nigra – Grade III, 0.59 cm².

≤0.20 cm², whereas an area of SN ≥ 0.25 cm² was assessed as pathological.

An area of SN between 0.20 and 0.25 cm² was assessed as a borderline value11.

The second possibility of TCS is in evaluating echogenicity of SN on a five-grade scale12 – Table 2. Echogenicity SN higher than grade II and area ≥ 0.25 cm² was considered pathological. In our study, we evaluated the area and echogenicity of SN in 111 patients of PD. A hyperechogenic SN grade more than II and area ≥ 0.25 cm² were detected in 84.7 % of PD patients19.

Berg et al. studied6 the relationship between SN echogenicity and motor symptoms in an elderly population (56–70 years). They evaluated 330 patients and concluded that a hyperechogenic SN was often connected with bradykinesia, rigidity and higher age (over 60). We obtained very similar results in our study in a group of 202 patients with movement disorders. Hyperechogenic and enlarged area of SN were significantly more frequent in patients with symmetrical bradykinesia and rigidity20. A subsequent study showed that a hyperechogenic SN is enlarged contralaterally to manifest parkinsonian symptoms21.

However, in 8-10 % of healthy subjects, a hyperechogenic SN can be detected. Recent 18F-DOPA (18F-fluorodopa) PET studies have revealed a marked decrease in
the accumulation of $^{18}$F-DOPA in the sample studied. Although the examination of motor function was normal, it was suspected that there was a subclinical alteration of the striatonigral system.

Walter et al. investigated a group of patients with idiopathic PD and patients with non extrapyramidal symptoms. The results of the study show that bilaterally enlarged hyperechogenic SN is probably a marker of idiopathic PD. A hyperechogenic SN was detected in 45% of the relatives of patients with idiopathic PD. Moreover, in asymptomatic subjects with the Parkin mutation, a correlation was found between enlarged hyperechogenic SN and striatonigral alterations in PET studies.

Subsequent work detected a hyperechogenic SN in patients with olfactory dysfunction together with dopamine reuptake alteration on SPECT (123-FP-CIT) in 70% of examined patients.

Unipolar depression in Parkinson’s disease

Depression and anxiety are very frequent symptoms in PD with a prevalence of about 40%. They are probably related to the role of the brainstem in regulating mood and cognition. Becker et al. evaluated brainstem changes related to the role of the brainstem in regulating mood in PD with a prevalence of about 40%. They are probably neuroleptic blockade of dopaminergic factor. On the other hand, free iron in the human body is toxic given its ability to form free radicals. Ferrous ion Fe$^{+}$ can generate the highly toxic hydroxyl and superoxide free radicals or molecular oxygen.

Ferritin is a storage protein of iron in the tissues and is important for blood formation. It is present in the normal axon. Recent studies reported on two cases of L-ferritin gene mutations. These mutations are associated with degeneration of the basal ganglia and occur in families. The disorder is termed hereditary ferritinopathy. The first published work failed to confirm more frequent occurrence of these mutations in patients with PD or increased SN echogenicity.

Ferroxidase ceruloplasmin (Cp) is involved in iron metabolism. It is produced by the spleen and secreted into the blood. By oxidizing the ferrous Fe$^{+}$ form of iron to the ferric Fe$^{+++}$ form, Cp promotes iron loading onto transferrin. In this way, Cp is an effective antioxidant and prevents oxidative damage to proteins, lipids and DNA. Cp is also produced by astrocytes in the brain, cerebellum, retina and epithelial cells of the choroid plexus. Astrocytes produce a special form of ceruloplasmin, which is connected to the membrane by glycosylphosphatidylinositol (GPI). This form of Cp plays a very important role in iron homeostasis and antioxidant processes in the brain.

Studies of patients with aceruloplasminemia, who have hereditary ceruloplasmin gene mutation, show that in these patients, iron accumulates in various organs, e.g., liver and brain. Iron deposits lead to neurodegeneration and expression of neurological symptoms – motor incoordination, parkinsonism, dementia and other medical disorders, such as diabetes mellitus.

Hochstrasser et al. examined mutation of Cp gen in 176 PD patients. D554E with I63T mutation was found in PD patients with hyperechogenic SN, whereas R793H mutation was also detected in the normal population with a hyperechogenic SN. Furthermore, this study shows a correlation of Cp and formation of Lewy bodies. Pilot was evaluated using TCS after stereotactic injection of different concentrations of iron or ferritin, zinc and 6-OHDA (6-OH-dopamine) together with desferrioxamine. The iron content in the SN was assessed using spectroscopy and the echogenicity of SN was measured as well. Increasing iron content increased the echogenicity of SN.

It is possible that a hyperechogenic and enlarged SN in atypical syndromes like MSA (multiple system atrophy) and VP (vascular parkinsonism) is caused by this mechanism. Reasons for development of variable iron metabolism impairments in these parkinsonian syndromes will be the topic of further research. Neuronal degeneration in the SN region could also be induced by toxic exposure to pesticides, heavy metals, by basal ganglia injury or by oxidative damage. The authors speculate about the possible contribution of pure SN atrophy.

Iron participates in various biological processes. It is an essential cofactor of many enzymes. Iron supports the transport of oxygen in hemoglobin and plays the main role in many oxidative and reduction processes as a cofactor. On the other hand, free iron in the human body is toxic given its ability to form free radicals. Ferric ion Fe$^{+++}$ can generate the highly toxic hydroxyl and superoxide free radicals or molecular oxygen.

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study shows the possibility of correlation of Cp ferroxi-
dase in blood and hyperechogenic SN39.
Neuromelanin is accumulated in SN pigmented
neurons with normal aging. Neuromelanin plays an
important protective role in inactivation of Fe** and re-
duced formation of free hydroxyl radicals, which other-
wise contribute to oxidative stress and neuronal death.
Neuromelanin could interact with many heavy metal ions,
e.g., zinc, copper, manganese or cadmium. In the course
of Parkinson’s disease and related syndromes, the concen-
tration of iron in the SN increases by 30-35 % (ref.33). In
contrast, neuromelanin in SN is decreased in PD patients.
This decrease could be caused by reduction of neuromela-
nin production or its higher degradation or higher sensi-
tivity of pigmented neurons to neurotoxins53. Zecca et al.
in post-mortem studies detected increased content of iron
in the hyperechogenic SN in 40 PD patients. A negative
correlation was found between hyperechogenic SN and neuromelanin content of SN33, 34.

Although the exact mechanism by which iron gets re-
distributed in various region of the brain is poorly under-
stood, it is known that brain cells in certain areas of the
brain have variable ability of to accumulate iron. It has
not been clarified whether this accumulation is caused by
primary accumulation of iron compounds in microglia
and macrophages or by iron accumulation in neurons33.

TCS evaluation in other movement disorders
Studies published so far demonstrate that changes
in SN echogenicity detected by TCS are not specific for
PD, but they are also more frequent in other movement
disorders than in a healthy population7, 8, 18. In addition
to the SN structure, TCS can be used to evaluate changes
in other structures – e.g., the lenticular nucleus, caudate
nucleus, cerebellum, width of the third ventricle or the
frontal horn of lateral ventricles (Table 2).

Multiple system atrophy, progressive supranuclear palsy and corticobasal degeneration
Enlarged and hyperechogenic SN on TCS examination
is not specific to PD. In patients with multiple system
atrophy (MSA), increased echogenicity and area of SN is
also seen. Behnk et al found hyperechogenic SN in 25 %
patients with MSA and medium echogenicity in another
37.5 % (ref.35, 36). In our group of patients with MSA, hy-
perchogenic SN (≥ grade III) was detected in 42.9 % and
medium echogenic (grade III) in 14.2 % patients. Enlarged
area of SN ≥ 0.25 cm² was found in 50 % patients39, 40.
Patients were selected using Quinn’s criteria37, 38.

Between 72 % and 82 % of patients with MSA also
have a hyperechogenic lenticular nucleus35, 36. Very similar
findings were described in patients with progressive sup-
ranuclear palsy (PSP)7, 39. Smaller studies reported that
echogenicity of SN and lenticular nucleus could distingui-
sh PN from MSA and PSP in more than 90 % of patients with
PSP39. Hyperechogenic SN was detected in 10/21 patients. This
finding did not correlate with the expression and severity
of neurological symptoms. In 19 patients, they detected
hyperechogenic LN, in 12 out of these patients this pathol-
ogy was also visible on MRI. A hyperechogenic thalamus
was detected in 9 patients, enlargement of the third ven-
tricle in 4 patients, enlargement of frontal horns of lateral
ventricles in 5 patients. Hyperechogenic LN and thalamus
correlated with expression and disease severity41.

The results of the pilot studies suggest the ability of
TCS to detect accumulation of copper in the basal ganglia
preclinically but the results must be confirmed in larger
patient population41.

Vascular parkinsonism
Tsai et al. (2007) studied hyperechogenic SN in 80
patients with PD in comparison with 30 patients with
vascular parkinsonism (VP) and 60 normal controls. A
hyperechogenic SN was present in 84 % of PD patients, in
20 % of VP patients and in 5 % of controls. 66.7 % of VP
patients had evident vascular changes on TCS evaluation
and their pulsatility index was significantly higher than in
PD patients and controls. There were no significant dif-
ferences in flow velocities between the VP and PD patients
and controls44.

In our pilot work44, we evaluated 11 patients with
VP using TCS. Patients were classified according to the vascular rating scale for the diagnosis of vascular parkinsonism\textsuperscript{45, 46}. Echogenicity and area of SN were higher in comparison with healthy population, but the results did not reach statistical significance. Hyperechogenic SN was detected in 18.2\% of cases and medium echogenicity in 45.4\%.

**Dementia with Lewy bodies**

Idiopathic PD and dementia with Lewy bodies (DLBD) are both characterized neuropathologically by the presence of Lewy bodies in various parts of the brain, especially in the brainstem, diencephalon, basal ganglia and neocortex. The presence of Lewy bodies is the main pathological substrate underlying cognitive dysfunction in PD and DLBD. Neuroimaging methods such as CT, MR and PET are not able to distinguish idiopathic PD from DLBD.

Walter et al. studied echogenicity of SN in patients with DLBD. Parkinson’s disease patients with dementia (PDD) and PD patients without dementia. Hyperechogenic enlarged SN was detected at least on one side in 97\% patients with DLBD, 97\% patients with PDD and 94\% patients with PD without dementia. Bilateral hyperechogenic SN was detected mainly in DLBD in 80\%. Only one third of PD patients had bilateral findings of hyperechogenic SN. In PND patients these findings were associated with the youngest age. An asymmetry index was ≥ 1.15.

PDD and DLBD patients could be discriminated by a combination of hyperechogenic enlarged SN, asymmetry index and onset age with a sensitivity of 96\% and specificity of 80\%, positive predictive value was 93\%. In patients with DLBD and PDD the width of the third ventricle and frontal horn was significantly larger than for PD patients without dementia. This enlargement correlated with UPDRS scale in PDD\textsuperscript{47}.

**Huntington’s disease**

Huntington’s chorea is a genetically caused neurodegenerative disease characterized by expansion of CAG triplets which leads to clinical symptoms. Postert et al.\textsuperscript{48} published the first results of TCS evaluation of patients with Huntington’s disease in 1999. In 40\% of their patients, a hyperechogenic SN (in 27\%) or caudate nucleus (in 13\%) was detected. No changes in the echogenicity of the thalamus or LN there were found. It is suspected that hyperechogenicity of the caudate nucleus is caused by gliosis or increase in metal concentration. Neuropathological studies have confirmed higher levels of iron and lower levels of ferritin in the caudate nucleus. Increase in copper concentration is probably responsible for the hyperechogenic SN\textsuperscript{49}.

**Spinocerebellar ataxia**

The results of a recent TCS study\textsuperscript{50} confirm that patients with genetically-proven spinocerebellar ataxia subtype 3 (SCA3) show hyperechogenicity of various brain structures, as do subtypes SCA1 and SCA2. Hyperechogenic white matter of the cerebellum was detected in 57\%, hyperechogenic dentate nucleus in 54\%, hyperechogenic SN in 40\%, hyperechogenic putamen in 40\% and hyperechogenic pallidum in 40\% patients. These were significantly higher than in the healthy population (p < 0.05). Moreover, cerebellar atrophy and enlargement of the fourth ventricle were detected in all patients with SCA3. Finally, the width of the third ventricle and the lateral ventricle were significantly larger than in the control group\textsuperscript{51}.

**Dystonia**

Dystonia is characterized by involuntary prolonged muscle contractions that distort the body into typical postures\textsuperscript{52, 53}. The pathogenesis of idiopathic dystonia and their origin is still unknown. It is known that the basal ganglia are the generator of dystonic movement. One of the pathological mechanisms described in the patients with idiopathic dystonia is increase in copper content in LN. Accumulation of copper probably causes disturbance of neuronal transfer from LN to motor cortex. The reason for copper metabolism impairment is unclear. Menkeson protein is the copper-transporting membrane ATP-ase and transports copper from cells outside. The results indicate that reduction of Menkeson protein gives rise to copper metabolism impairment and accumulation of copper in brain cells.

The first evaluation of dystonic patients using TCS were published by Naumann et al. in 1996 (ref.\textsuperscript{52}). Subsequent studies\textsuperscript{53} demonstrated that hyperechogenic LN is present in patients with torticollis or dystonic writer’s cramp on the contralateral side of rotation of the head or affected hand. This echogenicity is higher than in a normal population\textsuperscript{54}. A hyperechogenic SN was found in patients with facial dystonia only in 31\% (ref.\textsuperscript{52}). In practice, hyperechogenic LN could support the diagnosis of idiopathic dystonia and differentiate tardive dyskinesia and psychogenic dystonia.

**Restless leg syndrome**

The majority of patients with restless leg syndrome (RLS) have normal neurological findings on clinical examination and routine neuroimaging\textsuperscript{54, 55}. MRI studies which are able to quantify the concentration of iron in the brain of patients with RLS (according to criteria from the year 2003)\textsuperscript{55}, detected decrease of iron concentration in SN and putamen\textsuperscript{56}.

Two TCS studies reported a reduction in SN echogenicity in 82\% of patients with idiopathic RLS and 40\% with the secondary RLS. The detectable area\textsuperscript{56, 57} of SN was less than 0.1 cm\textsuperscript{2}. In both groups, the same pathological mechanism is suggested – iron homeostasis disorder in the brain\textsuperscript{56, 57}.

**Reproducibility of the sonographic evaluation**

Many studies have shown that TCS is a reliable method with high specificity and sensitivity in the diagnosis of PD\textsuperscript{14-18}. Correlations of SN evaluation were statistically significant (r = 0.8, Cohen’s kappa coefficient 0.83)\textsuperscript{5, 6}.

Our study focused on the inter-reader reproducibility of TCS evaluation and correlations in the assessment of
sonographic experience were low. Between sonographic lab assistant and physician without sonographic experience. Correlations between readers (intra-reader and inter-reader) and correlation between investigators (intra-investigator and inter-investigator) were assessed. Correlations between readers were \( r = 0.55-0.82 \) for evaluation of echogenicity and \( r = 0.31-0.74 \) for evaluation of SN area (p < 0.05).

Intra-reader correlations were significant only in an experienced sonographer (\( r = 0.85-0.96 \) for echogenicity and \( r = 0.51-0.69 \) for area SN, p < 0.001). Also all correlations between investigators (intra-investigator and inter-investigator) were significant as well for evaluation of area (\( r = 0.69-0.88 \) and \( r = 0.5-0.61 \)), as well as echogenicity SN (\( r = 0.64-0.92 \) and \( r = 0.51-0.69 \), p < 0.05). All 3 readers identified the same 15 patients with SN echogenicity III or more. It is known that semi-quantitative TCS evaluation of area and echogenicity of SN depends on sonographer experience. Only an experienced sonographer is able to achieve reliable results with statistically significant correlations. Correlations between sonographic lab assistant and physician without sonographic experience were low.

CONCLUSION

TCS is a very quick, non invasive and inexpensive examination method. It could be helpful in the differential diagnosis of movement disorders. The results depend on the examiner experience and quality of trans temporal bone window. Using TCS, we could also detect structural involvement of the nigrostriatal system in preclinical stages of other neurodegenerative disorders. Available pilot results of these observations are presently being replicated in wider patient populations.

ABREVIATIONS

APS – atypical parkinsonian syndromes
CBD – corticobasal degeneration
MSA – multiple system atrophy
NPV – negative predictive value
PD – Parkinson’s disease
PPV – positive predictive value
PSP – progressive supranuclear palsy
SD – standard deviation
Se – sensitivity
Sp – specificity
TCS – transcranial sonography
UPDRS – Unified Parkinson’s Disease Rating Scale

REFERENCES


