TRANSCRANIAL ULTRASOUND EXAMINATION OF THE BRAIN PARENCHYMA IN NEUROPSYCHIATRIC DISEASES

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Abstract

Transcranial sonography (TCS) is a highly sensitive non-invasive ultrasound method for the detection of early and specific echogenic changes in the basal ganglia (BG) of patients suffering from some neurodegenerative diseases. TCS showed *substantia nigra* hyperechogenicity as a typical echo feature in idiopathic Parkinson's disease (PD) and lenticular *nuclei hyperechogenicity* as a characteristic finding in atypical Parkinsonian syndromes. Discontinuity or hypoechoic appearance of the raphe is a common finding in patients with unipolar depression or depression associated with certain neurodegenerative disorders. TCS also shows hyperechoic changes in the basal ganglia in movement disorders associated with the accumulation of certain metals, such as Wilson's disease (WD), some neurodegenerative entities with metal accumulation, as well as in certain forms of spinocerebellar ataxia.

TCS is a reliable neuroimaging method for early differential diagnosis and monitoring of patients with neurodegenerative and psychiatric diseases.

Keywords: basal ganglia echogenicity, neurodegenerative diseases, psychiatric diseases, transcranial parenchymal sonography

Introduction

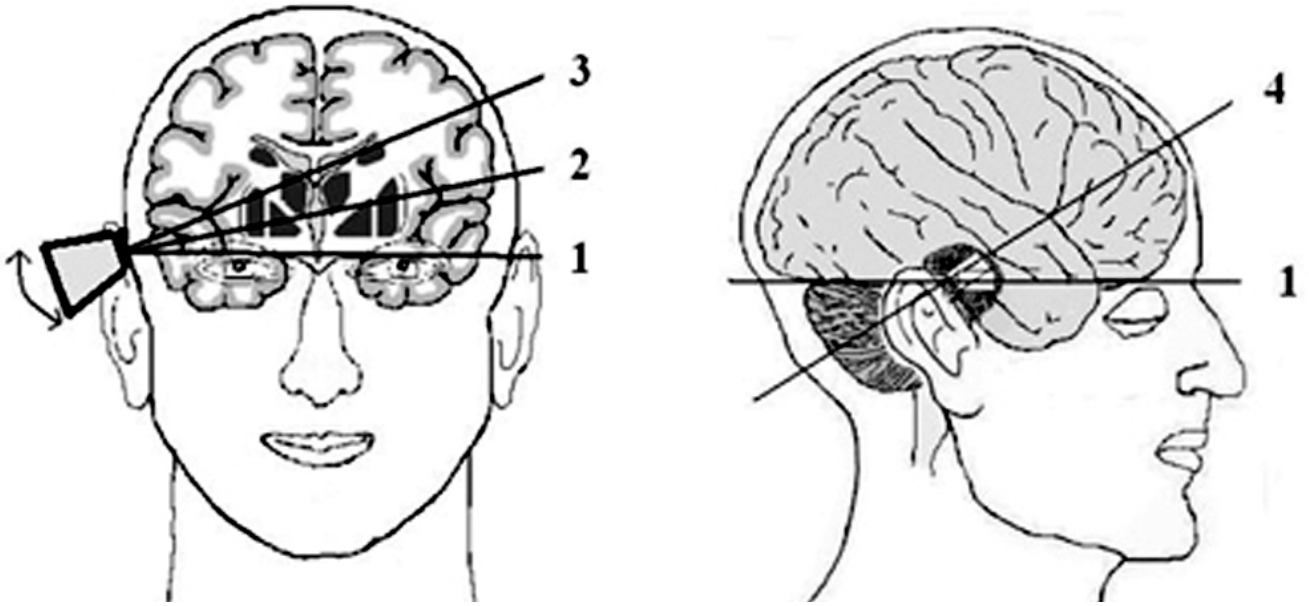
Transcranial parenchymal ultrasonography, in the diagnosis and differential diagnosis of neurodegenerative diseases and other movement disorders, is a method that has rapidly evolved in the past two decades. For many years, it was believed that the intact adult skull prevented the detection of pathological intracranial processes using TCS. In the early 1980s, research showed that transcranial ultrasound is useful in diagnosing hemodynamic changes in intracranial arteries (arterial stenosis, intracranial vasospasm, arteriovenous malformations)[1]. By the beginning of the next decade, transcranial Doppler became a key method for diagnosing acute and chronic cerebrovascular changes[2]. However, visualizing the brain parenchyma using TCS posed an even greater challenge. The structure of the skull requires the use of low-frequency ultrasound (up to 5 MHz), which limits the resolution of the obtained image. The first attempts to introduce transcranial sonography (TCS) into clinical practice date back to the 1970s. However, in the early 1990s, this diagnostic method began to develop rapidly. In 1995, Becker et al. used TCS to demonstrate specific ultrasonic changes in the substantia nigra (SN) region in patients with Parkinson's disease (PD), which was not possible with any other diagnostic method at that time[3].

The main advantages of transcranial sonography (TCS) over other neuroimaging methods are as follows: TCS is non-invasive, relatively easily accessible, easy to apply, and cost-effective for diagnosing neurodegenerative diseases. Patients are not exposed to radiation or radioactive substances, and the procedure can be repeated as needed, especially in patients with involuntary movements. The main disadvantages of TCS are related to the fact that the quality of results depends on the qualifications and experience of the person performing it, as well as the characteristics of the acoustic transcranial windows. In 10-20% of individuals of Caucasian race and even 20-40% of Asians, the acoustic windows may show either poor insonation or be completely non-transparent[4]. Despite these limitations, TCS demonstrates high sensitivity and specificity, which contributes to its significance as an additional diagnostic procedure in the diagnosis and differential diagnosis of neurodegenerative and some psychiatric disorders.

Ultrasonic systems and parameters for performing TCS

For TCS, the latest generation ultrasound machines and phased-array ultrasound probes with a frequency of 2-3.5 MHz are used. With these frequencies, the axial resolution is about 0.7 mm, while the lateral resolution depends on the width of the ultrasound beam and the depth of insonation, ranging from 2.2 to 3.8 mm. In parenchymal echo sonography, it is necessary to obtain well-modulated B-mode

Image 1. Schematic presentation of the plane of insonation in TCS



Explanation of picture 1. The ultrasound transducer is positioned in the temporal bone window parallel to the so-called orbitomeatal line, allowing visualization of structures at the level of the brainstem (1). By rotating the transducer approximately 10° cranially, structures at the level of the third ventricle are visualized (2). Further rotation of the transducer approximately 25° upward reveals the lateral ventricles and the medial wall of the lateral ventricles (3). By returning to plane 1 and tilting the dorsal part of the transducer downward by approximately 45°, followed by a slight rotation upward by about 10-15°, visualization of structures in the posterior fossa plane is achieved (4)[4]

images, which require a dynamic range of 50-55 dB and an insonation depth of 14-16 cm. The examination is performed according to a standard protocol in specific planes of insonation that are defined by specific ultrasound markers. There are three basic planes of insonation, and sometimes a fourth or cerebellar plane is used to detect the diameter of the fourth ventricle or hyperechoic zones in the cerebellum[4-9] (figure 1).

The examination is performed through a transtemporal approach by positioning the transducer on the anterior, middle, or posterior temporal ultrasound window, where the thickness of the bone is minimal, allowing easier penetration of the ultrasound beam. In clinical practice, the posterior temporal bone window is most commonly used as it provides the best visualization, especially of small structures such as the basal ganglia[4-10]. The examination begins by placing the ultrasound transducer in the transtemporal window parallel to the so-called orbitomeatal line. Figure 2 shows a B-mode image obtained as follows: a hypoechoic structure resembling a butterfly - the midbrain - surrounded by hyperechoic basal cisterns. The substantia nigra (SN), red nucleus (RN), and raphe are visualized as hyperechoic structures on the ipsilateral side. During the examination, attention should be paid to the penetrating arteries, which are also hyperechoic, as well as the demarcation between the SN and RN[4-10]. The B-mode image is magnified 3-4 times, and the outer border of the hyperechoic signal of the substantia nigra (SN) is outlined to obtain the surface area of the hyperechoic zone expressed in cm^2 (figure 2). It is considered that normal hyperechogenicity, which occurs as a result of the natural degeneration process of dopaminergic neurons in the SN, does not exceed 0.19 cm^2. Due to differences in ultrasound devices, each ultrasound laboratory is advised to establish its parameters for evaluating pathological hyperechogenicity of the SN and other structures of the basal ganglia. Hyperechogenicity of the SN below 0.19 cm^2 is considered normal, between 0.19 and 0.24 cm^2 is classified as moderate, while hyperechogenicity of the SN > 0.24 cm^2 is classified as marked.

The echogenicity of the *raphe nucleus* is evaluated after bilateral insonation. Normally, the raphe appears as a continuous line of high echogenicity that divides the *mesencephalon* into two peduncles. The echogenicity of the raphe is typically the same as the echogenicity of the RN or basal cisterns under normal circumstances. The latest recommendations include a two-step grading scale for raphe echogenicity. The scale has values of 0 and 1. A normal finding on at least one side of insonation is indicated by a score of 1. A pathological finding is indicated by a score of 0, which represents decreased echogenicity of the raphe, interruption of the raphe continuity, or complete absence of the signal during insonation on both sides[10-12].

The second level of insonation is at the level of the third ventricle (TV) and is visualized by rotating the ultrasound transducer approximately 10 degrees upward. The anechoic structure of the third ventricle is identified between two hyperechogenic lines that reflect the ependyma. On both sides of the third ventricle, there are hypoechoic structures representing the thalamus. At this level, the largest transverse diameter of the third ventricle (Trans D) and the frontal horn of the contralateral lateral ventricle is measured, starting from the ipsilateral to a contralateral inner surface of the hyperechogenic ependyma.

The normal values for Trans D are age-dependent and are as follows: < 7 mm for individuals aged 20-60 years and

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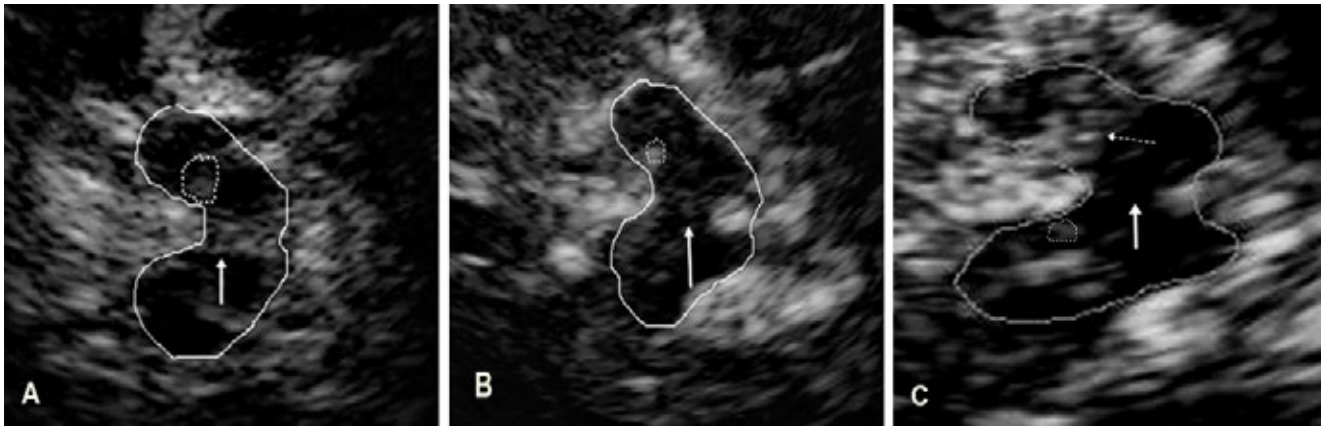
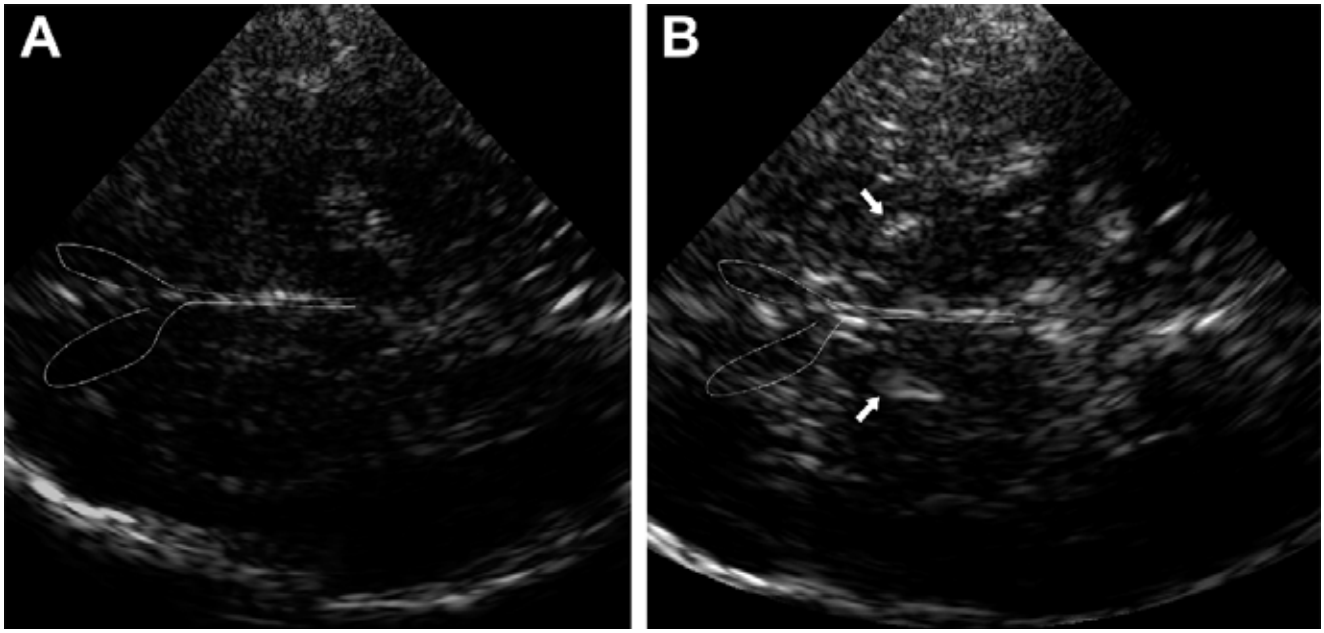
Image 2. TCS axial views at the brainstem level (insonation plane 1) of three different subjects



Explanation of picture 2. The hypoechoic structure of the *mesencephalon* in the shape of a butterfly is outlined with a solid line for better visualization. Thicker arrows indicate the raphe, and RN is depicted with a dashed line. **A)** *Mesencephalon* of a healthy individual with normal echogenicity of the raphe, appearing as a continuous hyperechoic line that is equally echogenic as RN; **B)** *Mesencephalon* of a patient with unipolar depression showing disruption of continuity and hypoechoic appearance of the raphe (grade 0); **C)** *Mesencephalon* of a patient with Parkinson's disease and depression, demonstrating pronounced hyperechogenicity of the substantia nigra (thinner dashed arrow on the side of insonation) and absence of the raphe signal (grade 0, thicker arrow)

Image 3. TCS image at the level of the third ventricle (level of insonation 2)



Explanation of picture 3. TV and frontal horns are depicted with dashed lines. **A)** In a healthy individual, there are no pathological hyperechoic signals at the level of the basal ganglia. **B)** Hyperechogenicity of both LN in one patient indicated by arrows, and the measurement of the hyperechoic area is usually performed contralateral to the insonation side[4]

< 10 mm for individuals aged ≥ 60 years. As for the diameter of the frontal horns of the lateral ventricles, the normal values are < 17 mm for individuals aged 20-60 years and < 20 mm for individuals aged ≥ 60 years. These values serve as reference ranges for assessing the size of these structures in TCS imaging.

At this level, the basal ganglia (caudate nucleus - CN and lentiform nucleus - LN), as well as the thalamus, are visualized. These structures are not normally visible as they are isoechoic with the surrounding brain parenchyma. In the case of the appearance of a hyperechoic signal, the planimetric measurement of the hyperechoic area is performed in the same way as explained for SN, and the presence of any hyperechoic signal in these structures is considered a pathological finding[10-12].

Sometimes a third axial plane is used to measure the diameter of the third ventricle (*cella media*) by tilting the transducer approximately 25° cranially. The measurement is performed between the inner surfaces of the ependyma, and information about the diameter of the *cella media* provides us with additional insight into the degree of brain atrophy.

TCS in neurodegenerative diseases

TCS u PD

In more than 90% of patients with idiopathic PD, a characteristic finding on transcranial sonography (TCS) is the hyperechogenicity of the substantia nigra (above the

pathological threshold)[4, 13]. Analyses have shown that the hyperechogenicity of the substantia nigra is primarily due to iron accumulation. It is still unknown at which point in the neurodegenerative process the accumulation begins, but the intensity of the hyperechogenic signal does not change with disease progression and is not correlated with the severity of clinical symptoms. Therefore, the hyperechogenic signal of the substantia nigra can also serve as an indicator of predisposition to PD development.

The hyperechogenic signal of the substantia nigra is also found in 10% of healthy individuals, but they are at a higher risk of developing PD later on. The finding of unilateral or bilateral hyperechogenicity of the substantia nigra above 0.19 cm^2 in asymptomatic patients can be evaluated as a preclinical marker of dopaminergic system dysfunction[4]. In newborns and children, hyperechogenicity of the substantia nigra is normally present but decreases over time, so it is not typically observed in individuals aged 16 and older[14]. The reason for this phenomenon is not clear. Although only 1-2% of the population over 60 years old develops PD, it is believed that around 10% of the population experiences presymptomatic stages of PD, which is consistent with the prevalence of hyperechogenicity of the substantia nigra in about 10% of the healthy population[5].

Atypical Parkinsonism and TCS

Atypical Parkinson's disease disorders represent the greatest differential diagnostic challenge compared to Parkinson's disease, especially in the early stages of the disease. These disorders include multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD). Many studies are based on the interpretation of different TCS parameters, which could facilitate the differentiation of this diseases[15]. Hyperechogenicity of the substantia nigra (SN), although considered a specific sign of Parkinson's disease, also occurs in a certain number of patients with other disorders that affect the SN and/or basal ganglia (BG).

This directly affects the specificity of the ultrasound findings. In this case, the specificity of the ultrasound finding indicates the probability that the test will be negative (not detecting SN hyperechogenicity) if the examined subjects are healthy[16]. Using parenchymal ultrasound, SN hyperechogenicity in MSA and PSP usually does not differ from the normal population (less than 0.19 cm^2), so the discriminative value of the method is very high, i.e., PD can be distinguished from MSA and PSP with up to 90% certainty. In the differential diagnosis between MSA and PSP, Trans D and hyperechogenicity of the LN have diagnostic value. In MSA, hyperechogenicity of the LN is registered and usually, the normal width of the third ventricle is less than 10 mm, while in PSP, hyperechogenicity of the LN is usually accompanied by dilation of the third ventricle.

By observing all three structures, the specificity and sensitivity of the findings are very high, around 90%[8-11]. In approximately 90% of CBD patients, bilateral hyperechogenicity of the substantia nigra with a normal width of the ventricular system (Trans D not exceeding 10 mm) is present. The discriminative value compared to PSP is also around 90%[5, 16]. Studies show a hyperechogenic signal in the area of the substantia nigra in 88% of cases, while in 83% of subjects, a hyperechogenic signal in the area of the *locus coeruleus* is detected, which can further help in the differentiation between PD and atypical parkinsonism[17].

TCS in diagnosing Wilson's disease

Wilson's disease (WD), or hepatolenticular degeneration, is a rare autosomal recessive disorder caused by mutations in the ATP7B gene, which is responsible for the synthesis of ceruloplasmin protein necessary for copper transport and its elimination from the body. In 40% of patients, the first symptoms originate from the liver, in another 40% of patients, neurological symptoms appear first, while in 20% of patients, behavioral and other psychiatric disorders are the initial manifestations. Neurological symptoms can include dysarthria, akinesia, dystonia, tremor, and ataxia. Magnetic resonance imaging (MRI) often reveals structural changes in the basal ganglia, caudate nucleus, ventral part of the thalamus, globus pallidus, mesencephalon, pons, and cerebellum, including the dentate nucleus, as well as atrophy of the white and gray matter of the cerebral cortex, but usually in later stages of the disease.

Only two studies have investigated basal ganglia lesions in a group of patients with Wilson's disease (WD). One study conducted by Valter and colleagues[18] included two groups of patients: 18 patients with neurological symptoms and three neurologically asymptomatic patients. Hyperechogenicity of the *locus coeruleus* (LN) was detected in all symptomatic patients and two out of three asymptomatic patients. The authors suggested that hyperechogenicity of the LN is most likely a result of copper accumulation rather than gliosis. Additionally, the size of the hyperechogenic zone in the LN correlated with the severity of symptoms and could expand to involve the thalamus and surrounding structures. A hyperechogenic signal of the substantia nigra (SN) was detected in 10 out of 21 (47%) patients with WD. However, it is crucial to differentiate between WD and other movement disorders, especially in younger patients, as specific therapy exists for WD and should be initiated as early as possible.

The second study, based on their data, included 54 patients who were clinically stable and classified as either predominantly neurological or hepatic symptom patients. TCS demonstrated a statistically significant higher prevalence of hyperechogenicity in the substantia nigra and *locus coeruleus* in patients with Wilson's disease compared to the control group[19]. Moderate hyperechogenicity of the substantia nigra was found in 31.5% of patients with Wilson's disease (42% with neurological symptoms and 7% with hepatic form of the disease) and in 8% of healthy controls. Hyperechogenicity of the *locus coeruleus* was detected in 81.5% of patients with the neurological form of the disease

and 6.7% of healthy controls. This study also demonstrated a correlation between disease severity and the degree of hyperechogenicity in the substantia nigra and the width of the third ventricle. The Trans D value is significantly higher in patients with the neurological form of the disease compared to those with the hepatic form[19], which is consistent with the claim that global brain atrophy exists in up to 90% of patients with Wilson's disease[20]. Both studies demonstrated the ability of TCS to detect copper accumulation, and possibly other metals such as manganese and iron, in the basal ganglia region of patients with Wilson's disease, even in the early stages of the disease and in neurologically asymptomatic patients. This finding has significant therapeutic implications.

TCS and other neurodegenerative diseases with movement disorders

TCS has also shown promising results in the diagnosis of several other neurodegenerative disorders characterized by movement disorders. Specific changes in TCS have been observed in some neurodegenerative diseases characterized by metal accumulation. Kostic et al. conducted MRI and TCS imaging in five patients suffering from neurodegeneration associated with pantothenate kinase, caused by a mutation in the gene encoding the enzyme pantothenate kinase 2 (PanK2). All patients had the characteristic "tiger's eye" sign on MRI, which refers to hypointense lesions limited to the globus pallidus (GP) and substantia nigra (SN). TCS revealed hyperechoic lesions limited to the lenticular nucleus (LN) and substantia nigra (SN), with normal Trans D values. Both MRI and TCS findings in patients with pantothenate kinase-associated neurodegeneration are consistent with pathological evidence of iron accumulation, even in advanced stages of the disease, predominantly affecting the GP and SN, suggesting selective involvement of these structures in the pathological process[21].

In patients with cervical and upper extremity dystonia, TCS shows increased echogenicity of the lenticular nucleus (LN), which is more pronounced on the contralateral side of the clinically affected area. The hyperechogenicity of the LV is likely a result of increased accumulation of manganese and copper[22].

Two studies have shown similar hyperechogenic changes in the basal ganglia in spinocerebellar ataxia (SCA) type 2 and type 3. Additionally, hyperechogenic lesions in the substantia nigra were a common finding in both studies, indicating an involvement of the nigrostriatal dopaminergic system in these patients. Hyperechogenicity of the substantia nigra was found in 66.7% of patients with SCA 2 and 73.3% with SCA 3, respectively[23, 24]. Patients with SCA 2 also had significant dilation of the ventricular system, reflected in the dilation of the third ventricle. Although evidence of TCS changes is limited, enlargement of the fourth ventricle and hyperechogenicity of the nucleus dentatus can be considered characteristic findings in SCA 3, as well as in SCA 17. Moreover, bilateral and particularly pronounced hyperechogenicity of the pallidostriatal regions has been described as a new diagnostic marker in sonographic differentiation of extrapyramidal and ataxic movement disorders[23, 24].

Although rarely reported, TCS also reveals changes in the basal ganglia in patients with Huntington's disease (HD)[25]. Hyperechogenicity of the SN has been associated with a more severe prognosis, and weaker cognitive abilities are associated with the enlargement of the ventricular system. Moreover, the assessment of the width of the frontal horns of the lateral ventricles using TCS accurately corresponds to their dimensions assessed by computerized tomography (CT). Symptoms of depression corresponded to abnormal echogenicity of the raphe mesencephalic structures. Additionally, a higher number of CAG (cytosine-adenine-guanine) repeats alleles corresponded to the presence of hyperechogenicity in the SN. Approximately 40% of HD patients show signs of hyperechogenicity in at least one region of the basal ganglia. Hyperechogenicity of the SN was found in 12 (26.7%) patients. Bilateral changes were found in 10 (83.3%) of them. The number of CAG copies is correlated with the hyperechogenicity of the SN. A hyperechogenic signal in the caudate nucleus (CN) was detected in 6 (13.3%) patients, and a hyperechogenic signal in the lentiform nucleus (LN) was detected in 3 (6.7%) patients. The echogenicity of the thalamic region was consistently normal[25].

TCS in the diagnosis of the most common disorders in the secondary parkinsonism

a) Vascular parkinsonism: In the elderly population, vascular changes in the brain arteries are commonly associated with Parkinson's disease (PD). However, in cases where parkinsonism is exclusively of vascular origin, hyperechogenicity of the substantia nigra (SN) is not typically detected in the majority of cases[26]. Normal echogenic signal of the SN and atherosclerotic changes in brain blood vessels detected by color Doppler provide strong evidence in favor of vascular parkinsonism. However, it should be noted that 10% of healthy individuals exhibit hyperechogenicity of the SN, and its incidence increases with age. Therefore, hyperechogenicity of the SN does not necessarily indicate idiopathic PD[27], while a normal finding of the SN likely excludes a neurodegenerative cause of parkinsonism in favor of a vascular etiology.

b) Secondary parkinsonism caused by manganese accumulation: It most commonly occurs with chronic exposure to manganese, often observed in miners. So far, only one case study involving two patients has been published, showing normal echogenicity of the substantia nigra and hyperechogenicity of the lenticular nucleus, suggesting that the striatum is the preferred site for manganese deposition[28].

c) Hemochromatosis: a disease characterized by iron accumulation, and it is believed that it does not affect the central nervous system, due to the blood-brain barrier. However, in a slightly higher proportion of cases compared

to the general population (10%), hyperechogenicity of the substantia nigra can be detected in these patients (14%). Additionally, the hyperechogenicity of the lenticular nucleus is more pronounced in these patients[29].

TCS in depression and differential diagnosis of depression

Numerous studies have demonstrated the involvement of the limbic system and *raphe nuclei* in the pathogenesis of depression. An ultrasound marker that can be useful in the diagnosis and differential diagnosis of depression is the change in echogenicity and continuity of the raphe. Hypoechogenicity of the *raphe nuclei* is present in unipolar depression (in 50-70% of patients) as well as depression associated with Parkinson's disease (in over 85% of patients). However, in healthy individuals, bipolar affective disorders, schizophrenia, depression in multiple sclerosis, and Parkinson's disease without associated depression, the echogenicity of the *raphe nuclei* is preserved. It is hypothesized that the hypoechogenicity of the *raphe nuclei* may be caused by modifications in cell density in the brain parenchyma, changes in the composition of the interstitial matrix, or damage to the integrity of nerve fibers and tracts[10]. Studies have shown that reduced echogenicity of the *raphe nuclei* is common in depressive disorders, regardless of the diagnostic category of depression, while this finding is rare in healthy individuals without a history of any psychiatric disorders. However, the echogenicity of the *raphe nuclei* is not a marker that can aid in differentiating different categories of depressive disorders. Additionally, changes in the echogenicity of the *raphe nuclei* are associated with the response to Selective Serotonin Reuptake Inhibitors (SSRI) therapy. Hypoechogenicity of the *raphe nuclei* is more pronounced in SSRI responders compared to non-responders. Hypoechogenicity of the *raphe nuclei* indicates a good response to SSRI therapy with a positive predictive value of 88%[9, 10].

TCS and depression in PD

Several TCS studies have shown that depression in Parkinson's disease, as well as unipolar depression, is likely associated with structural lesions of the *raphe nuclei*. Hypoechogenicity of the *raphe nuclei* is a common finding in depressive patients with PD. In comparison to non-depressed patients, where the hypoechogenic signal of the *raphe nuclei* is detected in only 6-27% of cases, depressive patients with PD exhibit hypoechogenicity of the *raphe nuclei* in 35-85% of cases[10, 30-32].

The initial studies have shown that the echogenicity of the *raphe nuclei* is significantly reduced in depressive patients with PD compared to healthy controls and PD patients without depressive symptoms (more than 90% of depressive PD patients had hypoechogenic *raphe nuclei*)[33]. The echogenicity of the *raphe nuclei* negatively correlated with the degree of motor disability in PD patients with comorbid depression. Studies have also demonstrated that the hyperechogenicity of the substantia nigra (SN), which is a characteristic finding in idiopathic PD, is common in depression. Among depressive individuals without parkinsonism, pronounced SN hyperechogenicity was found three times more frequently compared to age-matched healthy individuals. Hypoechogenicity of the *raphe nuclei* was significantly more common in depressive patients regardless of the presence of PD. The combination of pronounced SN hyperechogenicity and reduced echogenicity of the *raphe nuclei* is significantly associated with a history of depressive disorder before the onset of PD, as well as with motor asymmetry in depressive individuals without PD.

In patients with PD and comorbid depression preceding the onset of motor symptoms of PD, there was more pronounced hyperechogenicity of the substantia nigra, and it was correlated with an earlier onset of PD[33].

On the other hand, a significant reduction in the echogenicity of the raphe nucleus has been found in patients with PD who had symptoms of irritative bladder compared to those without these symptoms. Hypoechogenicity of the raphe nucleus was associated not only with irritative bladder symptoms but also with the presence of dysthymia and major depression. This finding does not solely indicate a direct association between raphe nucleus damage and irritative bladder or depression symptoms but also suggests the possibility of underlying damage in another brain region that is connected to the raphe nucleus via afferent pathways[34].

Although several studies have shown alterations in the MR signal of the raphe nucleus in depression, a characteristic neuroimaging pattern of raphe abnormalities in depression has not been established yet. However, the published findings so far provide important evidence of structural and functional changes in the raphe nucleus as a possible etiopathological factor in depression. A study that compared findings on T2-weighted MRI sequences and the echogenicity of the brainstem identified a correlation between raphe nucleus echogenicity and changes in brain MR signal intensity, suggesting the presence of structural damage to the brainstem in depression comorbid with PD, similar to unipolar depression[31]. These findings suggest that reduced raphe nucleus echogenicity and increased signal intensity in T2-weighted MRI may reflect disruption or damage to myelinated monoaminergic pathways (dopaminergic, serotonergic, or noradrenergic) passing through the brainstem and raphe nucleus[10, 31].

The fact that TCS shows a fairly specific finding in patients with PD makes this method unique in the differential diagnosis of depression, PD, and the concurrent occurrence of both disorders. In PD, the characteristic hyperechogenicity of the substantia nigra can be visualized in the early stages of the disease, even before the onset of motor symptoms, enabling early clinical diagnosis. The simultaneous presence of SN hyperechogenicity and depression may have important etiological implications and potential implications for the later development of symptoms.

Sometimes it is clinically challenging to differentiate between depression as an early marker of PD, unipolar depression, and depression associated with PD. The value of TCS in the differential diagnosis between PD and depression is most evident in the earliest stages of the disease when isolated clinical characteristics cannot distinguish whether the patient has PD or depression[10]. However, even in the later stages of PD where hypomimia and bradykinesia can mimic a depressed mood, TCS findings can be very useful. In individuals with isolated depression, most cases show normal echogenicity of the substantia nigra (SN) with a hypoechoic or interrupted/undetectable raphe. In patients with PD, normal echogenicity of the raphe is observed alongside SN hyperechogenicity. In patients with both PD and concomitant depression, pathological findings are usually present: SN hyperechogenicity and raphe hipoechoicity. It should also be noted that patients with isolated depression without any signs of concurrent PD may have significant SN hyperechogenicity[30]. This can be explained by the fact that depression is often a premotor marker for PD, suggesting that individuals with depression and SN hyperechogenicity are at an increased risk of developing PD later in life. Differential diagnostic challenges can arise in depressive patients with motor slowing who exhibit both SN hyperechogenicity and raphe hipoechoicity. If antidepressant therapy is introduced to such patients, and it proves successful in treating their symptoms, it indicates isolated depression. However, depression can also manifest as a premotor symptom of PD, wherein the hyper-echogenicity of the substantia nigra represents a risk factor for PD[4, 5, 10, 35]. Therefore, the simultaneous occurrence of substantia nigra hyper-echogenicity and raphe hypo-echogenicity in individuals with depression or very mild motor symptoms may indicate that this population is at risk of developing PD. Based on current knowledge and observations, it appears that raphe hypo-echogenicity is not only useful in the differential diagnosis and early detection of depression but may also be valuable, especially in combination with substantia nigra hyper-echogenicity, in identifying individuals at risk of developing PD.

TCS and bipolar disorder

Bipolar disorders are characterized by alternating episodes of depression and mania or hypomania. Histological studies have revealed subtle structural abnormalities in the dorsal parts of the raphe, as well as a regional reduction in noradrenaline synthesis. Initial ultrasound studies showed normal or increased echogenicity of the baroreceptor region (BR) in patients with bipolar disorders. This led to the conclusion that decreased raphe echogenicity (grade 0) could be specific to unipolar depression[10]. A study conducted later demonstrated raphe hypo-echogenicity in 36.1% of patients with bipolar disorder. The ultrasound findings did not differ across different mood phases in bipolar disorder. Raphe hypo-echogenicity correlated with the severity of depressive symptoms in bipolar disorder. Additionally, bipolar patients generally exhibited significantly wider brain ventricles compared to healthy individuals.

Hyperechogenicity of the SN in healthy individuals

Cross-sectional studies have shown that substantia nigra hyperechogenicity occurs in as many as 10-15% of healthy individuals[36-38]. It has been demonstrated that first-degree relatives of individuals with PD exhibit SN hyperechogenicity in over 40% of cases. This may affect the specificity of SN hyperechogenicity as a marker in PD diagnosis, therefore other parameters for PD diagnosis should be carefully considered if a positive finding is obtained in individuals without clinical symptoms of the disease[39, 40]. Numerous studies have shown that individuals without clinical symptoms but with SN hyperechogenicity may suffer from depression[7, 10,] and olfactory dysfunction[38]. Similarly, they are more likely to experience severe symptoms related to the extrapyramidal pathway due to neuroleptic use[41], while approximately 60% of cases may exhibit reduced uptake of neurotransmitters in the nigrostriatal system[37, 38, 42].

Conclusion

Transcranial sonography is a relatively new diagnostic procedure that will continue to evolve in the future. TCS results can certainly aid in the differential diagnosis of Parkinson's disease PD compared to other neurodegenerative disorders that clinically present in a similar manner but exhibit changes in different brain structures. TCS can provide particular benefit in the early diagnosis of clinically unmanifested cases, primarily in patients who are at an increased risk of developing a neurodegenerative disorder. Based on previous research, it is clear that TCS can be successfully used as a complementary diagnostic procedure to other neuroimaging methods such as CT and MRI. However, like any other method, TCS has certain limitations that need to be considered in everyday clinical use and interpretation of the obtained results.

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