Transcranial Ultrasound in movement disorders - a review

A Ultrassonografia nos Transtornos do movimento – uma revisão

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ABSTRACT

Background Transcranial Sonography (TCS) is a neuroimaging method at the neurologist's fingertips. The most widely recognized application of sonography of the brain parenchyma is the diagnosis and differential diagnosis of Parkinson's disease (PD). Improvements in the B-mode (bidimensional) technique allied to advances in signal processing have refined the image resolution allowing many specific brain structures to be studied with the method.
Objectives In this paper we will provide up-to-date information about main uses of TCS in the diagnostic approach of patients presenting with different movement disorders.
Methods We performed a comprehensive literature review about the researches on the main applications of TCS for neurological practice focussing on parenchymal evaluation in movement disorders.
Results We describe the main findings of TCS in PD, Essential Tremor, Progressive Supranuclear Palsy, Multiple System Atrophy, Lewy Body Disease, Drug-induced parkinsonism, Vascular parkinsonism, Normal Pressure Hydrocephalus, Wilson's disease, Huntington's disease and cerebellar ataxias.
Conclusions TCS has collected significant attention in Neurology due to its non-invasiveness, safety, and cost-effectiveness. We reviewed high quality TCS research that showed good sensitivity and specificity in diagnosing movement disorders. Although still restricted to research centers around the world, TCS has the potential to become a practical diagnostic screening tool for neurologists, particularly in resource-limited settings where other imaging modalities may not be available.

Keywords Neuroimaging; Transcranial Doppler Ultrasonography; Diagnostic imaging; Central Nervous system diseases; Movement Disorders

RESUMO

Fundamento A ultrassonografia transcraniana (UTC) é um método de neuroimagem ao alcance do neurologista. A aplicação mais amplamente reconhecida da ultrassonografia do parênquima cerebral é o diagnóstico e o diagnóstico diferencial da doença de Parkinson (DP). A evolução da técnica do modo B (bidimensional) aliada aos avanços no processamento de sinais refinaram a resolução da imagem, permitindo que muitas estruturas cerebrais específicas fossem estudadas com o método.
Objetivos Neste artigo fornecemos informações atualizadas sobre os principais usos da UTC na abordagem diagnóstica de pacientes que apresentam diferentes transtornos do movimento.
Métodos Realizamos uma ampla revisão da literatura sobre as pesquisas com as principais aplicações da UTC para a prática neurológica com foco na avaliação do parênquima cerebral nos transtornos do movimento.
Resultados Descrevemos os principais achados da UTC na DP, Tremor Essencial, Paralisia Supranuclear Progressiva, Atrofia de Múltiplos Sistemas, Doença de Corpos de Lewy, Parkinsonismo induzido por drogas, Parkinsonismo Vascular, Hidrocefalia de Pressão Normal, Doença de Wilson, Doença de Huntington e Ataxias cerebelares.
Conclusões A UTC tem recebido atenção significativa devido à sua não-invasividade, segurança e custo-benefício. Revisamos pesquisas de alta qualidade com a UTC que mostram boa sensibilidade e especificidade no diagnóstico de alguns transtornos do movimento. Embora ainda restrita a centros de pesquisa em todo o mundo, a UTC tem potencial para se tornar uma ferramenta prática de triagem diagnóstica para neurologistas, especialmente em ambientes com recursos limitados, onde outras modalidades de imagem podem não estar disponíveis.

Palavras-chave Neuroimagem; Ultrassonografia Doppler Transcraniana; Diagnóstico por imagem; Doenças do Sistema Nervoso Central; Transtornos do movimento

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INTRODUCTION

Transcranial B-mode sonography (TCS) is a neuroimaging method that visualizes the brain parenchyma and intracranial ventricular system through an intact skull. Modern TCS systems are now capable of providing higher-resolution images of echogenic deep brain structures compared to MRI under clinical conditions as already demonstrated by Walter et al. (2008)[1]. As TCS is based on different physical principles than other imaging techniques, i.e. reflection of ultrasonic waves at tissues with different impedances, TCS can offer unique and complementary information on brain tissue pathology.

TCS has evolved as a diagnostic tool for movement disorders over the past three decades[2]. The most widely recognized application of TCS is the diagnosis and differential diagnosis of Parkinsonian syndromes. Many research groups around the world have confirmed that hyperechogenicity of the substantia nigra (SN) in brain sonography can serve as a sensitive and fairly specific marker of Parkinson's disease (PD) [3,4,5] . Practically speaking, a patient at first neurological evaluation for Parkinsonian symptoms in whom a TCS examination finds no SN hyperechogenicity, deserves further investigation for diseases other than idiopathic Parkinson's.

Moreover, improvements in the B-mode technique allied to advances in signal processing have refined the image resolution of the brain parenchyma in ultrasonography [6,7,8]. Nowadays, investigators analyze other specific brain structures in TCS exams, besides SN echogenicity, that add in the differential diagnosis. For example, enlarged ventricles call attention to normal pressure hydrocephalus while hyperechogenicity of basal ganglia nuclei may suggest an atypical parkinsonism. Finally, allying B-mode sonography to Doppler sonography that investigates vascular intracranial arteries flow characteristics may be useful in those cases of suspected vascular parkinsonism [7,9] . The specific advantages of TCS are the relatively low costs of technical equipment, its wide availability, the short investigation time, its non-invasiveness, bedside availability and little corruption by patients´ movements. Additionally, the learning curve of the method is reasonably short, circa six to eight months, making it feasible for interested neurologists[10]. So, it is a neuroimaging method at the neurologist´s fingertips.

In this paper we will provide up-to-date information about the main uses of TCS in the diagnostic approach of patients presenting with different movement disorders in ambulatory scenarios.

METHODS

We performed a comprehensive literature review about the applications of TCS on neurological clinical practice focusing on parenchymal evaluation in movement disorders in outpatient settings. The terms *Diagnostic Sonography, Transcranial Sonography, Atypical parkinsonisms and Movement disorders* were searched alone or in combination in the databases of BIREME, PubMed and Lilacs.

RESULTS

The results were organized in the items: (1) TCS in Parkinson's Disease; (2) TCS in the differential diagnosis of PD from Essential Tremor (ET), Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA) and Lewy Body Disease (LBD); (3) TCS in the diagnosis of drug-induced parkinsonism; (4) TCS in the diagnosis of Vascular Parkinsonism (VP); (5) TCS in the diagnosis of Normal Pressure Hydrocephalus (NPH); (6) TCS in the diagnosis of Wilson´s disease (WD); (7) TCS in the diagnosis of Huntington´s disease (HD) and (8) TCS in the diagnosis of cerebellar ataxias.

1. TCS in Parkinson's Disease (PD)

PD is a debilitating neurodegenerative disorder that primarily affects motor function, causing symptoms such as bradykinesia, asymmetric resting tremor and rigidity. Transcranial sonography (TCS) has emerged as a valuable diagnostic tool for the detection of PD due to its non-invasiveness, cost-effectiveness, and portability. The hallmark of PD diagnosis using TCS is the hyperechogenicity of the SN (SN+), which has been shown to have high sensitivity (S) and specificity (E) for PD diagnosis [2,4,6,11] .

The "hyperechogenic" SN means that the structure has an enlarged echogenic area on TCS, usually above a cut-off at 0.20 cm^2 [1]. SN hyperechogenicity is frequently greater contralaterally to more intense symptoms but can be ipsilateral. It is enough to obtain one SN with an echogenic area above the cut-off to classify the exam as abnormal. This echo signal has been reported to be independent of motor severity or disease evolution, but this stability has been recently questioned as newer studies have found a positive association between the SN area and long-lasting disease[12]. Nonetheless, the exam is considered not useful for patient follow-up, except to monitor ventricle enlargement in patients with long-term illness and cognitive decline [13,14] .

[1]For a detailed description of the Method in transcranial sonography, see a previous paper on this issue of RBN.

A meta-analysis found a good diagnostic accuracy of TCS for PD, with sensibility ranging from 71% to 92% and specificity ranging from 86% to 100%[3]. A more recent systematic review and meta-analysis found a pooled S= 83% and a pooled E= 87% in studies of PD patients compared to healthy controls. The positive likelihood ratio, the negative likelihood ratio and diagnostic odds ratio were calculated as 6.94, 0.19 and 42.89 respectively[4]. This diagnostic accuracy refers to the presence only of SN hyperechogenicity in the exam of a patient. The presence of other sonographic signs besides SN+ such as ventricle enlargement, hyperechogenicity of lentiform nucleus or mesencephalic atrophy, for example, suggest an alternative diagnosis to idiopathic PD.

In 10-15% of healthy individuals we can also find a hyperechogenic SN. Some studies argue that a SN+ can be present in pre-symptomatic people with subclinical striatal dysfunction. A longitudinal European study found that the sonographic marker was associated with an increased chance for developing PD in some SN+ individuals[15].

TCS also shows good accuracy to distinguish PD from parkinsonisms or other diseases. A meta-analysis of 168 published reports about differential diagnosis between PD and other movement disorders found a 94% mean accuracy value (S=85%, E=71%)[5]. Another meta-analysis compared TCS accuracy to SPECT (single photon emission computed tomography) using [123I] FP-CIT (123I-ioflupano), commercialized as DaTScan[16]. TCS exhibited a S=50% and E=82% to differentiate PD from healthy controls, whereas SPECT showed S=97% and E=100%. Nonetheless, in the differentiation between PD and atypical parkinsonism, TCS had a S=50% and E=43% versus S=97% and E=0% of SPECT. The predictive value for an abnormal TCS to predict an abnormal SPECT was 88%. The study's main conclusion was that TCS has a high screening value before the molecular method, a more expensive and invasive examination.

Also, combining markers enhances our ability to diagnose PD. A study compared TCS plus myocardial scintigraphy with MIBG (*Metaiodobenzylguanidine*) or an olfaction test to differentiate PD from atypical parkinsonisms[16]. Methods accuracy were respectively 74% for TCS, 80% for MIBG and 75% for hyposmia. But, when hyposmia and TCS are combined, E reaches 98% for diagnosing PD[18]. A recent Brazilian study found that TRODAT (scintigraphy with 99mTC with high affinity to dopamine transporter protein) exhibits a 90% accuracy versus 79.2% of TCS and 85.5% for olfaction evaluation[19].

An interesting and difficult situation in clinical practice occurs when patients with high suspicion for a PD diagnosis have all molecular exams negative for dopaminergic deficit. They are called patients with SWEDD (*Scans Without Evidence of Dopaminergic Déficit*). In the ELLDOPA study, even after 4 years of follow-up these SWEDD patients still had negative molecular exams and a negative TCS as well[20].

In conclusion, TCS remains a useful screening neuroimaging method in the investigation of patients with a parkinsonian syndrome. A SN+ is suggestive of PD with an overall 80-90% accuracy. Although molecular imaging methods display higher specificity, they are not widely available and are not risk-free. The strategies of combining TCS with other methods such as olfaction evaluation are a valid choice.

2. TCS in the differential diagnosis of PD from Essential Tremor (ET), Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA) and Lewy body disease (LBD))

Table summarizes the main findings and accuracy of TCS in the differential diagnosis of Parkinsonisms. Besides the high accuracy of SN+ in the diagnosis of PD, it has also demonstrated high accuracy in differentiating PD from ET and good accuracy for atypical Parkinsonian syndromes, such as PSP and MSA. This can be achieved by integrating sonographic analysis of SN echogenicity + basal ganglia echogenicity + mesencephalic area + ventricular width[7,21]. The evaluation of all these structures[2] increases TCS accuracy as SN+ can be found in 20-30% of atypical parkinsonisms and in ET.

Table – TCS accuracy in the differential diagnosis of Parkinsonisms

	Indicated condition	Excluded condition	Sensitivity	Specificity
SN+	PD	Heatthy or ET	78-100%	81-92%
SN+	PD	MSA or PSP	82-98%	70-100%
SN- and LN+	MSA or PSP	PD	56-59%	99-100%
SN-	Second. Parkinsonism; ET	PD	80-88%	91%
3rd V (>10mm) and LN+	PSP	PD	84%	98%
LN+ and 4th V (>10 mm)	MSAc	PD	unknown	unknown
Asymmetry index ≥1,15	PDD	LBD	69%	80%
Onset index >35,5	LBD	PDD	96%	80%

*Adapted from Pilotto 2015; Walter 2006
Asymmetry index = (larger SN ÷ smaller SN); ET = essential tremor; LN+ = hiperechogenicity in lentiform nucleus;
LBD = Lewy body dementia; LN+ = hiperechogenicity in lentiform nucleus;
nset index = ((age of disease onset x sum of echogenic area of bilateral SN) ÷ asymmetry index))
PD = Parkinson´s disease; PDD = Parkinson´s disease dementia; SN+ = substantia nigra hyperchogenicity
(area > 0,20 cm²); 3rd v = third ventricle; 4th V = fourth ventricle

An important differential diagnosis for tremor-dominant PD is ET. An early correct diagnosis is of cardinal importance, as prognosis and management differ considerably among these conditions. Several studies have shown a much lower prevalence of SN+ in ET patients, from 8 to 16%, than in PD patients, who show SN+ in 71-92%. The presence of hyperechogenic SN excludes ET with a high predictive value (81-92%)[22,23]. However, some investigators argue that those ET patients with SN+ might correspond to

[2]For a detailed description of the Method in transcranial sonography, see a previous paper on this issue of RBN.

a group with an increased risk to develop PD in the future [24].

Regarding the differential diagnosis between PD and PSP, the detection of SN+ plus mesencephalic atrophy and 3rd ventricle enlargement is also documented as highly specific to PSP cases (Table). Although there is no cut-off score established for normal mesencephalic area, a study found it to be > 4.0 cm² in 90% of healthy individuals[2]. So, the finding of an enlarged SN echogenic area plus a mesencephalic area below 4.0 cm² is a red flag to a possible PSP diagnosis. Besides, these patients usually have a large 3rd ventricle diameter, above 1.0 cm. The detection of a hyperechoic lentiform nucleus adds to accuracy in the diagnosis of an atypical parkinsonian syndrome as it is seldom found in idiopathic PD.

The differentiation between MSA and PD by TCS relies in the detection of a hyperechogenic focus on lentiform nucleus (LN+) that shows an accuracy rate, specificity, PPV, and NPV of 81.0%, 74.0%, 92.5%, and 49.3%, respectively [21,25]. Especially in the MSA subtype with cerebellar involvement (MSA-C), a large 4th ventricle in the posterior fossa reinforces the MSA-C suspicion.

Patients with LBD exhibit SN+ in TCS with a similar frequency to PD patients, indicating a common etiology. However, they usually have bilateral larger SN areas, above 0,25 cm² that are relatively symmetrical. A study that evaluated SN in LBD *versus* dementia in idiopathic PD revealed that an asymmetry index ≥1.15 in the echogenic SN size, estimated by dividing the largest SN by the smallest, was found in 69% of patients with PD dementia. So, the more asymmetric the SN areas of a patient, the more likely a diagnosis of PD dementia. This TCS finding corresponds to the clinical picture of greater symmetry of motor symptoms in LBD, opposite to the asymmetry of PD motor symptoms[26].

Another study examining the role of TCS in the differential diagnosis between DLB and PD dementia created an index that considers the patient age at disease onset and the echogenic SN area bilaterally. This *Onset Index* is calculated with the formula: ⟪(age of disease onset x sum of echogenic area of bilateral SN) ÷ asymmetry index⟫. An OI >35.5 suggests LBD and not dementia in PD[27].

In summary, although a SN+ can also be found in up to 30% of atypical parkinsonisms, the presence of other echo signals, like hyperechogenicity in lentiform nucleus, reduced mesencephalic area or enlargement of 3rd or 4th ventricle, increase the likelihood of a non-PD diagnosis. In patients with Parkinsonism plus dementia, symmetrical higher values of SN area suggest LBD instead of PD dementia.

3. TCS in the diagnosis of drug-induced Parkinsonism

TCS has been investigated in the differentiation of drug-induced Parkinsonism from degenerative Parkinsonism. Studies indicate tha t the absence of SN hyperechogenicity (SN-) has a S=80-88% for drug-induced Parkinsonism. On the contrary, the presence of a SN+ has a negative predictive value for secondary Parkinsonism of 78-87%[28]. However, some studies show that a few patients initially diagnosed with drug-induced Parkinsonism show a hyperechogenic SN[29]. It is hypothesized that these patients have subclinical dopaminergic insufficiency as part of a latent degenerative Parkinsonism, and that the medication has exacerbated or accelerated the dopaminergic deficiency 30. This hypothesis aligns with clinical data indicating that about 20% of patients with medication-induced parkinsonism maintain or worsen symptoms despite discontinuing the causative drug even for long periods of time[31]. Another interesting finding was that patients with schizophrenia who develop moderate to severe parkinsonism associated with neuroleptic use have more frequent SN+ compared to patients with schizophrenia with mild or no parkinsonian signs[32].

In summary, the absence of SN hyperechogenicity (SN-) has a 78% accuracy rate in identifying cases of drug-induced Parkinsonism. Patients with drug-induced Parkinsonism that display SN+ may have a higher risk of developing PD in the future. More research on this topic is needed.

4. TCS in the diagnosis of Vascular Parkinsonism

Vascular Parkinsonism (VP) is secondary to cerebrovascular disease (CVD) and corresponds to 2.5%-5% of all Parkinsonisms. In general, VP begins later than idiopathic PD, but clinically they can be very similar and, sometimes, overlapping. The exact physiopathology of VP is not well established, but neuroimaging and pathological correlation to clinical data show that strategic infarcts or extensive white-matter disease account for it. It is assumed that white matter lesions interrupt the extrapyramidal thalamocortical motor pathways or the putamino-pallidal-thalamic pathway[32].

Clinically, Parkinsonism secondary to CVD is symmetrical, predominates in the legs and shows marked gait disturbance with postural instability and a tendency to falls (“lower half Parkinsonism”). Frequently there are pyramidal signs and dementia. These patients present more vascular risk factors compared to PD patients, such as dyslipidemia, systemic hypertension, smoking and a history of stroke. The sonographic examination of patients with VP displays no SN hyperechogenicity. On the other hand, Doppler analysis of middle cerebral arteries (MCA) frequently finds an elevated pulsatility index (PI) >1.04 and an elevated resistive index (RI) > 0.60, both indicating small vessel disease[33].

PD and VP are distinct illnesses with their own diagnostic criteria[34]. Although still controversial, some authors have found a positive relation between the

existence of risk vascular factors and altered brain hemodynamics in idiopathic PD, specifically its akinetic-rigid phenotype[35]. These findings may suggest that some PD phenotypes may correlate most with vascular disease, have a worse prognosis and, perhaps, require different treatment approaches.

In summary, a VP patient will typically exhibit normal SN echogenicity in TCS, and an altered Doppler signal of MCA with high resistance and pulsatility values, indicative of diffuse small vessel disease.

5. TCS in the diagnosis of Normal pressure hydrocephalus (NPH)

NPH is a potentially reversible syndrome characterized by gait disturbance, mental deterioration and urinary incontinence. Image findings of ventriculomegaly and normal cerebrospinal fluid pressure on lumbar puncture suggest the diagnosis. Following surgical CSF shunt treatment the symptoms may improve, notably the gait disorder. The differential diagnosis includes neurodegenerative conditions such as atypical Parkinsonism (especially PSP), Alzheimer's disease or dementia with Lewy bodies[36,37].

According to international guidelines, the following key imaging features should be employed for the diagnosis of NPH: (1) ventricular enlargement with Evan´s index >0.3 (the ratio of maximum width of the frontal horns of lateral ventricles and maximal internal diameter of skull at the same level on axial CT or MRI images); (2) absence of macroscopic obstruction to CSF flow; (3) at least one of these supporting features: a) enlarged temporal horns of lateral ventricles without hippocampal atrophy, b) callosal angle ≥40º, c) periventricular signal changes due to altered brain water content, d) flow void in the Sylvian aqueduct or 4th ventricle on MRI[36].

Although TCS findings are not diagnostic for the condition, they can be helpful in the right clinical context. In a patient above 60 years old with Parkinsonism, the finding of ventricular enlargement on a TCS exam, such as a 3rd ventricle width above 1.0cm and lateral ventricles width above 2.0cm[3], suggests hydrocephalus; if the patient presents with urinary incontinence, cognitive decline and a non-parkinsonian gait disturbance, the diagnosis of NPH is very likely.

6. TCS in the diagnosis of Wilson's Disease (WD)

Wilson's disease (WD) is a hereditary ailment that arises from mutations in ATP7B, which results in the accumulation of copper throughout the body. This disorder often manifests as early-adulthood Parkinsonism, and its atypical cases can be challenging to differentiate from early-onset PD (EO-PD), a neurodegenerative condition that occurs in individuals ≤40 years old.

The presence of hyperechogenicity in the lentiform nucleus (LN+) is the hallmark of WD in TCS. It persists even after two years of treatment to reduce copper accumulation. SN+ is less common and decreases after the initiation of treatment[38]. In a study, TCS showed significantly higher prevalence of SN+ (p=0.007) and LN+ together (p=0.001) in WD patients compared to controls. Disease severity correlated with SN+ (r = 0.303; p = 0.029) and with the 3rd ventricle width (r=0.351; p=0.011)[39].

A published work analyzed the diagnostic accuracy of TCS to distinguish EO-PD from WD and found that the "mean SN echogenicity index" i.e., the sum of both SN echogenic areas, was considerably higher in EO-PD than in WD and control participants[40]. Conversely, the mean lentiform nucleus (LN) echogenicity index was greater in WD compared to EO-PD and control subjects. So, using these indexes to diagnose WD, the authors found SN+index to have a S=93.8% and an E=90.9% and for LN+index a S=95.5% and an E= 93.8%. Interestingly, LN hyperechogenicity was more pronounced in WD subjects with putaminal MRI T2 hyperintensity but was also present in WD diagnosed subjects without MRI abnormality. The authors suggest that TCS could be a more precocious marker[40].

In summary, WD patients exhibit SN and LN hyperechogenicity. The sum of both SN echogenic signals is larger in EO-PD while the sum of both LN echogenic signals is larger in WD. These echographic signals seem to help to differentiate these conditions in young age. More research on TCS accuracy for these diseases is needed.

7. TCS in the diagnosis of Huntington's Disease (HD)

HD is an inherited progressive neurodegenerative disorder characterized by abnormal movements (chorea), psychiatric problems (depression) and dementia. It is inherited in an autosomal dominant pattern by a CAG trinucleotide repeat expansion in the huntingtin gene on chromosome 4p. Age of onset ranges from childhood to the eighth decade but is more common in mid-life. Age of onset before 20 years of age is considered juvenile HD or the Westphal variant, in which parkinsonism is sometimes the presenting symptom. Older adult patients can sometimes also present with signs of parkinsonism without tremor.

Hyperechogenicity of the substantia nigra (SN+) can be found in 66.4% of HD patients. Changes in the basal ganglia echogenicity were also associated with both depressive and motor symptoms in Huntington's patients[41]. Hyperechogenic caudate nucleus has also been described in the disease [42]. But frontal horn enlargements with a loss of their normal comma-shaped contour are the

[3]For a detailed description of the Method in transcranial sonography, see a previous paper on this issue of RBN.

most typical finding in TCS of HD. Irrespective of patients age, lateral ventricles width above 2.0 cm are usually found [43].

TCS evaluation of echogenicity of the mesencephalic raphe[4] correlates with depressive states. In Huntingtonian patients, raphe hypoechogenicity (absent or interrupted when insonated by both sides) was found in 78% of those with current symptoms of depression, in 57% with a previous history of depression, and in 56.8% with no signs or history of depression[41]. The HD patients with hypoechogenic raphe in TCS also had significantly higher depression levels as measured by the BDI (Becker depression inventory).

In summary, in TCS of Huntingtonians one can find SN and caudate nucleus hyperechogenicity, frontal horns enlargement and an absent or interrupted mesencephalic raphe.

8. TCS in the diagnosis of Cerebellar ataxias

Cerebellar ataxias are a rare and diverse group of neurodegenerative conditions affecting the cerebellum and its pathways. The autosomal dominant group or spinocerebellar ataxias (SCA) also presents non-cerebellar signs that may include extrapyramidal features such as rigidity, bradykinesia and pyramidal signs. In some cases, even peripheral nerve pathology can be found. It is important to differentiate sporadic adult-onset ataxia from atypical parkinsonism such as MSA-C (multiple system atrophy-cerebellar phenotype), which may present some overlapping clinical features.

Only a small number of articles describe TCS characteristics of patients with neurodegenerative ataxias. Parkinsonism as a dominant clinical phenotype has been described in SCA 2 patients, and pathological findings frequently reveal marked degeneration of the SN besides severe neuronal loss in the pons, cerebellum, inferior olive and dorsal columns. A recent study from Serbia found a significant correlation between SN hyperechogenicity and extrapyramidal signs (rigidity, dyskinesia and dystonia)[44]. In patients with SCA 2, SN+ has been detected in 67% with a correlation to extrapyramidal signs [5,44] .

SCA 3 (Machado-Joseph disease) is also characterized by ataxia and variable signs of parkinsonism, dystonia and peripheral neuropathy. A marked SN hyperechogenicity was also reported in this group of patients [44,45] . An enlargement of 3rd and 4th ventricles that correlated to ataxia severity was also found [44]. A Brazilian study found that the presence and severity of restless legs syndrome (RLS) in SCA 3 is inversely correlated with SN echogenic area, suggesting that RLS is linked to an iron-depleted state in these patients [46].

In patients with SCA-2 and SCA-3, alterations of ventricle size are invariably present. Also, a positive correlation between the TCS-evaluated diameters of the 3rd and 4th ventricles and the scores of severity of ataxia could be found[44]. The measurement of the brain ventricles (lateral, 3rd and 4th) by TCS has clinical significance in the estimation of hydrocephalus and its progression, as well as the estimation of cortical and cerebellar atrophy.

The most common form of autosomal recessive ataxia is Friedreich´s disease (FRDA), frequently beginning in adolescent years. The major clinical manifestations are neurologic dysfunction, cardiomyopathy and diabetes mellitus. Research investigating TCS characteristics in FRDA evidenced enlargement of ventricular diameters, but no SN+. Investigators found that these patients exhibit hyperechogenicity of cerebellar dentate nucleus (DN+) in 85% of the cases [45]. A relative increase in iron concentration in a degenerating DN was suggested as an explanation for this sonographic finding. TCS demonstrated that this process is specific to the DN, as none of the other structures investigated exhibited hyperechogenicity.

In summary, when investigating ataxias with TCS one should expect the finding of ventricular enlargement, especially the 4th ventricle, SN hyperechogenicity in SCA 2 and 3, and dentate nucleus hyperechogenicity in FRDA.

Future perspectives

Future perspectives in TCS examination for movement disorders and other neurodegenerative diseases are promising, driven by advancements in device sophistication. Research focusing on the precocious diagnosis of some rare conditions as Wilson´s or Huntington´s disease may add to clinical practice as the exam is harmless and cost-effective. New technologies for evaluating the echogenicity of structures, such as quantifying the tone of the pixels in the digitized image, can bring advances in the method's performance and increase its diagnostic accuracy for different conditions, especially for posterior fossa pathology.

CONCLUSIONS

TCS has collected significant attention in Neurology due to its non-invasiveness, safety, and cost-effectiveness. We reviewed high quality TCS research that showed good sensitivity and specificity in diagnosing neurological disorders, demonstrating a high value as a screening diagnostic tool. Specifically for PD and its differential diagnosis, the method has already proved its

[4]For a detailed description of the Method in transcranial sonography, see a previous paper on this issue of RBN.

good accuracy as a first-line, outpatient care neuroimaging diagnostic method that can be used by the neurologist itself in an ambulatory scenario. TCS has the potential to become a critical diagnostic tool, particularly in resource-limited settings where other imaging modalities may not be available.

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