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Transcranial ultrasound in adults and children with movement disorders

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Summary Since the first discovery, that ultrasound can overcome the skull allowing examination of the intracranial blood-flow as well as the first description of substantia nigra (SN) signal alterations via B-mode sonography, a plethora of applications especially in the field of movement disorders have been fostered. Up to now, however, most studies investigated adult individuals, even though numerous of the diseases studied have their onset already during childhood or adolescence. This overview summarizes recent studies of transcranial B-mode sonography (TCS) within the movement disorder field and outlines potential implications for pediatric applications.

History of transcranial ultrasound

For decades it was thought, that it is impossible to penetrate the intact scull by ultrasound for the visualization of intracranial structures and measurement of blood flow in the circle of Wilis. It was in the 1980s when Aaslid et al. could demonstrate that blood flow of the intracranial arteries can be analysed by transcranial Doppler sonography [1]. In following years a rapid development of ultrasound systems evolved until Becker et al. were able to display the substantia nigra (SN) reproducibly via B-Mode sonography in 1995. Moreover, they were able to demonstrate an enlargement and hyperechogenicity of the SN area patients suffering from Parkison's disease (PD) [2]. Up to now, this finding was reproduced by many independent groups and transcranial B-mode sonography (TCS) developed into an expanding research field for a multitude of medical applications. Here, we will shortly highlight the different ultrasound implementations in the medical field and will focus on the most recent advances in the diagnosis of movement disorders especially in children.

Current applications in adults

Applications in Parkinson's disease

In recent years, TCS has become widely accepted and used in the early and differential diagnosis of Parkinson's disease. One hallmark of this method, besides its inexpensiveness and non-invasive character, is the ability to discriminate between essential tremor, Parkinson's disease related tremor and the differentiation of atypical Parkinson syndromes [3—5]. In PD, the typical finding is a hyperechogenicity of the SN, which is normally more pronounced contralateral to the clinically more affected side [6]. This hyperechogenicitiy seems to stay constant during the course of the disease and patho-anatomical investigations revealed that it most likely reflects increased iron content, as was

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shown in animal experiments, as well as in post mortem of brains [7—10].

In patients with atypical signs in Parkinson syndromes TCS is useful for assignment to the idiopathic forms. Patients with multi system atrophy, or supranuclear palsy of the Richardson subtype do normally not display a hyperechogenic SN, but rather show increased echogenicity of the lenticular nucleus [5]. In contrast, patients with corticobasal degeneration commonly display a hyperechogenic SN in combination with hyperechogenicity in the lenticular nucleus [11].

Other movement disorders

In clinical practice, B-mode sonography proved also to be useful for discrimination of IPS from other movement or gait disorders, such as normal pressure hydrocephalus or other disorders associated with metal accumulation in the basal ganglia.

B-mode sonography allows the visualization of the ventricular system, especially the third ventricle and the side ventricles. Thus, in patients with an unclear gait disorder the differential diagnosis of a normal pressure hydrocephalus can be ruled out easily [12]. Due to the fact, that iron accumulation is proposed to be the anatomical correlation of the SN hyperechogenicity in Parkinson's disease, TCS was also studied in other movement disorders related to metal accumulation. For example, it was found, that the lenticular nucleus displays increased echogenic values in patients suffering from Wilson's disease, a disorder with copper accumulation in and outside the brain. The intensity of hyperechogenicity correlates with disease severity [13]. In patients with cervical and upper limb dystonia TCS displays increased lenticular nucleus echogenicity pronounced contra lateral to the clinically affected side [14,15]. As hyperechogenicity in the parenchymal sonography was believed to be due to metal accumulation, a post mortem analysis was performed in individuals suffering from dystonia. This study could rule out an increased copper and manganese content in the lenticular nucleus compared to controls [16]. Recently, our group was able to show, that patients suffering from neurodegeneration with brain iron accumulation (NBIA), a disease with childhood onset which is caused by mutations in enzymes dealing with iron metabolism in the brain, also shows increased echogenicity in the SN compared to healthy controls [17].

Taken together, TCS seems to be a valid tool in the differential diagnosis of movement disorders, especially if they are related to metal accumulation in the brain. In comparison to MRI findings especially in patients suffering from Wilson's disease and NBIA, it has to be critically noted that the sonographic findings do concur, but especially within the basal ganglia. MRI scans by far show more affected areas than sonography does [18] [19]. For example in Wilson's disease, T2-weighted MR images show decreased signal intensities in the globus pallidus, putamen, substantia nigra, and caudate nuclei, while TCS only verifies changes in the lenticular nucleus. Similar to Wilson's disease, T2*-weighted scans in NBIA show hypointensities within the globus pallidus, SN, putamen and the dentate nucleus. It is not clear so far, why not all signal abnormalities documented by MRI can be reproduced by TCS. One reason may be higher sensitivity of MRI in the detection of metal deposition. On the contrary, changes seen in the SN by TCS in PD in our experience occur earlier than those seen by MRI. In conclusion, one may speculate, that the sensitivity of TCS differs in various brain regions with some shortcomings within the basal ganglia region.

Movement disorders in children

In the pediatric field, besides CCT and cMRI, transcranial ultrasound is already used routinely for several years due to its advantages regarding radiation exposure and the ability to examine the children without sedation. The American Academy of Neurology and the Practice Committee of the Child Neurology Society thus recommend the use of TCS for neonates with an increased risk for intraventricular hemorrhage, preterm white matter injury or ventriculomegaly [20]. However until now routine use of ultrasound in children and adolescents with movement disorders is not widely applied. In light of the TCS findings gained from studies in adult patients with movement disorders we will highlight in the following three diseases displaying TCS abnormalities in adults with disease onset already during childhood or adolescence. As already mentioned above, Wilson's disease is a disorder with copper storage abnormalities throughout the body and also in the basal ganglia due to mutations in the copper transport ATPase [21]. Besides other symptoms, accumulation of copper in the brain leads to dystonia, tremor and akinetic-rigid symptoms with the age of manifestation ranging from 7 to 37 years of age. Some cases have been reported though with even earlier onset at preschool age [22,23]. The broad range of symptoms, which occur during disease course can cause difficulties in the early diagnosis. Prashanth et al. analysed the clinical data of Wilson's disease patients which were registered over 30 years and found a mean time delay from disease onset to diagnosis of two years with a range from 0.08—30 years [24]. Besides clinical experience and education, these data underline the need for diagnostic modalities in the early diagnosis of this disorder. As the MRI displays typical signs (e.g. ''face of the giant panda'' and the ''bright claustrum'') in this disease, it appears as one of the most important diagnostic tools in differential diagnosis. However, especially in children, MRI examination is laborious and most of the children need sedation [18]. This is, besides the costs, a limiting factor of this method and highlights the necessity for the implementation of a screening method. Walter et al. demonstrated typical changes in the lenticular nucleus by TCS with increasing echogenicity depending on the disease activity in Wilson's disease patients [13]. These results raise the hope, that TCS can be useful as a screening method in addition to copper and ceruloplasmin analysis in serum.

A second movement disorder with adolescent onset is Friedreich's ataxia. It is the most common among the inherited ataxias in Europe. The main clinical features are dysarthria, pyramidal tract damage and progressive ataxia [25]. The first clinical symptoms of Friedreich's ataxia normally appear during puberty, but also early and late onset variants exist [25]. To date, the diagnosis is based on clinical examination, supported by electrophysiological findings and

proven by genetic analysis with confirmation of a GAA expansion within the first exon of the Frataxin gene [26]. Recently Synofzik et al. published their study, which examined TCS in patients suffering from Friedreich's ataxia. Interestingly they could show hyperechogenic changes in the dentate nucleus, which was present in 85% of all patients and already visible after short disease duration [27]. This finding was accompanied by a hypoechogenic SN. One possible explanation for the hyperechogenicity of the dentate nucleus as discussed by the authors is an increased iron content, which is also detectable on T2*-weighted MRI images [28]. The authors see TCS useful for assessment of patients suffering from ataxia. One shortcoming is, that dentate nucleus hyperechogenicity is not specific for Friedreich's ataxia, but was also found in patients suffering from spinocerebellar ataxia type 3 (SCA3) [29]. In contrast to Friedreich's patients though, the hyperechogenicity appeared less frequent (54%) and in combination with SN hyperechogenicity (40%). Taken together, these two studies provide evidence for the usefulness of TCS in the differential diagnosis of ataxias, but further studies are needed to validate these data, especially a direct comparison of patients with Friedreich's ataxia to those suffering from SCA3 are needed to rule out the real diagnostic potential of TCS.

Neurodegeneration with brain iron accumulation, formerly known as Hallervorden—Spatz syndrome is a movement disorder with early onset and a wide range of initial neurological symptoms. The estimated prevalence is 1—3 per million. Neuropathological hallmarks are abnormal iron accumulations especially in the globus pallidus and the substantia nigra pars reticulata. Recently, mutations in the pantothenate kinase 2 (PANK2) gene were identified as causative for up to 70% of all NBIA cases. Hence, this subtype of NBIA was designated pantothenate kinase-associated neurodegeneration (PKAN) [30,31]. The first symptoms usually occur during childhood and patients initially present with walking difficulties. Later the typical symptoms consisting of dysarthria, dystonia and visual problems occur [32]. To date, the diagnosis is obtained using MR imaging showing the pathognomonic hypointensity within the globus pallidus along with high signal intensity in the center of the globus pallidus internus also known as ''eye-of-the-tiger-sign'' (EOT-sign) on T2-weighted images [33]. The verification of the diagnosis is done by documentation of PANK2 mutation. As the clinical presentation of patients can be unspecific and the MR imaging implies sedation in children, we recently performed a study examining the diagnostic properties of TCS in the diagnosis of NBIA. In this small study, 7 patients were examined by transcranial ultrasound and the results were compared to age matched controls without any history of neurological disease [17]. Interestingly, we found a highly significant hyperechogenicity of the SN in NBIA patients. Surprisingly, we were not able to detect valid changes within the basal ganglia, which in MRI usually display the pathognomonic EOT sign. As already discussed for Wilson's disease, further studies and more experience are needed to evaluate this shortcoming of TCS in the area of the basal ganglia. Due to the limited size of our study the findings need to be reproduced in a bigger cohort of patients. Nevertheless, it provides good evidence for the usefulness of TCS especially in children with suspected movement disorders prior to genetic testing or MR imaging.

Conclusion

Since the initial finding by Becker and co-workers, that TCS is capable of displaying changes in the SN in PD patients, the application of this method in the early and differential diagnosis of Parkinson related movement disorders is already part of the basic diagnostics in the clinical setting. To date, intensive research is examining the properties of this method in various diseases, especially in those where metal accumulation is causative or a result of the disorder. Unfortunately, this research usually is performed and focussed on adults. Because of the simplicity of this method, the ability to use it in patients without sedation and the lack of side effects a broader application is desirable with special focus on the pediatric field.

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