Review article

The role of neuroimaging in the diagnosis of the atypical parkinsonian syndromes in clinical practice

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ABSTRACT

Atypical parkinsonian disorders (APD) are a heterogenous group of neurodegenerative diseases such as: progressive supranuclear palsy (PSP), multiple system atrophy (MSA), cortico-basal degeneration (CBD) and dementia with Lewy bodies (DLB). In all of them core symptoms of parkinsonian syndrome are accompanied by many additional clinical features not typical for idiopathic Parkinson's disease (PD) like rapid progression, gaze palsy, apraxia, ataxia, early cognitive decline, dysautonomia and usually poor response to levodopa therapy. In the absence of reliably validated biomarkers the diagnosis is still challenging and mainly based on clinical criteria. However, robust data emerging from routine magnetic resonance imaging (MRI) as well as from many advanced MRI techniques such as: diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), voxel-based morphometry (VBM), susceptibility-weighted imaging (SWI) may help in differential diagnosis. The main aim of this review is to summarize briefly the most important and acknowledged radiological findings of conventional MRI due to its availability in standard clinical settings. Nevertheless, we present shortly other methods of structural (like TCS – transcranial sonography) and functional imaging (like SPECT – single photon emission computed tomography or PET – positron emission tomography) as well as some selected advanced MRI techniques and their potential future applications in supportive role in distinguishing APD.

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1.   Introduction

The term atypical parkinsonian disorders (APD) refers to a heterogeneous group of neurodegenerative movement disorders such as: progressive supranuclear palsy (PSP), multiple system atrophy (MSA), cortico-basal degeneration (CBD) and dementia with Lewy bodies (DLB). In all of them parkinsonism is accompanied by additional features (not typical for idiopathic Parkinson's disease) like rapid progression, gaze palsy, apraxia, ataxia, early cognitive decline, dysautonomia and usually poor response to levodopa therapy [1]. Although the diagnosis is based on clinical criteria the differential diagnosis at early stages is still challenging. It was shown in the clinical-pathological studies that even 24% of the patients with parkinsonian syndromes can be misdiagnosed [2]. Structural (magnetic resonance imaging – MRI or transcranial sonography – TCS) or functional neuroimaging (single photon emission computed tomography – SPECT or positron emission tomography – PET) may enhance the accuracy of the clinical diagnosis for parkinsonisms [3]. However, imaging studies are not required to make a diagnosis of PD or APD (with exceptions of regional cerebral blood flow SPECT – rCBF SPECT – with occipital hypometabolism as a supportive feature to confirm DLB [4] and MRI changes in recent Gilman's criteria for MSA [5]). Computed tomography of the brain is generally not useful, and may serve as a screening tool to rule out other pathologies such as tumors, chronic subdural hematomas or normal pressure hydrocephalus [6]. According to European Federation of Neurological Societies (EFNS) guidelines routine 1.5 T MRI is a method recommended to exclude symptomatic causes of parkinsonisms, but it may be useful in differentiating PD from APD [4,7]. TCS is another technique which has been proven to be reliable and useful in the differential diagnosis of parkinsonian syndromes [7]. All these structural imaging methods can be supplemented by nuclear imaging techniques (SPECT, PET), which provide additional information on brain metabolism and perfusion [8].

2.   Technical aspects of selected MRI modalities

Two major kinds of MRI abnormalities seen in parkinsonian syndromes are: atrophy – best seen in – T1W and changes of tissue signal – in T2W [9]. The latter depends on the specificity of the degenerational process. The accumulation of paramagnetic substances (e.g. iron) triggers the decrease of signal, which is observed, for example, in the basal ganglia due to the accumulation of ferritin. These changes are best seen when T2-weighted gradient-echo imaging is used, which indicates that this sequence has a special diagnostic value for parkinsonian disorders [10]. On the other hand, the increase of the signal in T2-weighted images reflects the myelin pathology such as Waller's degeneration, demyelinisation and gliosis of white matter tracts which are seen as hyperintensive changes [6].

As it has already been mentioned, this review focuses mainly on routine MRI as it is considered a basic ancillary test in diagnosing APD [2]. However, some advanced techniques are mentioned and characterized here shortly as well, since a lot of recent reports highlighted their growing role in diagnosing APD. At present, these techniques are still being evaluated and are not used in clinical practice, but we can expect a robust progress in that field in the near future. The most common are: diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), voxel-based morphometry (VBM), susceptibility-weighted imaging (SWI) [11]. DWI and DTI are techniques based on the random movement of water molecules, which is increased in the degenerated tissues due to the distraction of fibers, which in normal conditions limits the process of diffusion [1]. Quantification of diffusion is performed by calculation of the apparent diffusion coefficient (ADC) [12]. SWI is a new MRI technique which exploits the magnetic properties of iron content in tissues [13]. VBM is an operator independent, semi-automated technique which allows to assess quantitatively the regional cerebral atrophy [14]. H-MRS allows to monitor biochemical structure of tissues in vivo. It is based on the analysis of the ratio of metabolites such as: NAA (N-acetylaspartate) – as a marker of cells integrity, Cho (choline) – which is a phospholipid involved in the cells' membranes synthesis and a marker of their disintegrity, Cr (creatine) – marker for energy metabolism and myo-Ins (myo-inositol), which is a marker of glial cells with increased levels being associated with gliosis [8,14].

In general, it is considered that the conventional 1.5 T MRI images of PD patients, including T1W (T1-weighted images), T2W (T2-weighted images), T2 FLAIR (Fluid Light Attenuation Inversion Recovery) and proton density sequences do not show any abnormalities and do not differ from the controls [15,16]. Nevertheless, a lot of the characteristic radiological features have been described, which help to distinguish PD, PSP, MSA and CBD patients, some of them have their acknowledged position in supporting the clinical diagnosis and can be quite easily used in everyday radiological practice. This short review aims to summarize the most important, evidenced radiological signs of APD. The utility of those signs is assessed with the use of terms such as: sensitivity, specificity and positive predictive value. Sensitivity is the proportion of true positives – patients with the disease and with the abnormal finding in the radiological imaging. Specificity is the proportion of true negatives – healthy people without the abnormal findings in MRI. The positive predictive value (PPV) is the likelihood of the person with the abnormal finding in MRI to have the disease [17]. This review summarizes neuroimaging methods helpful in differential diagnosis of APD, and is mostly focused on standard MRI protocols as the method is used commonly in everyday practice.

3.   Atypical parkinsonian syndromes

3.1.   Progressive supranuclear palsy

PSP known also as Steele–Richardson–Olszewski disease is the most common of the parkinsonian taupathies [18] with a prevalence of 0.97–6.54 cases per 100 000 [19]. Its classical variant, called Richardson syndrome, PSP-RS, is characterized

by severe postural instability accompanied by early falls, supranuclear gaze palsy, dysarthria, axial rigidity, symmetric bradykinesia and dementia with pronounced frontal syndrome [20,21]. In the recent years several other phenotypic variants of PSP, varying in the clinical features, severity and pattern of atrophy have been described: PSP-PAGF (pure akinesia with gait freezing), PSP-PNFA (PSP with progressive non-fluent aphasia), PSP-C (PSP-cerebellar), PSP-CBS (PSP-corticobasal syndrome) [22]. Neuronal degeneration in PSP affects many areas of the brain: midbrain, superior cerebellar peduncle [23–25], subthalamus, pallidum, dentate nucleus, frontal lobes [26]. The radiological abnormalities are related to these pathological findings [27]. The midbrain atrophy with the enlargement of the third ventricle is regarded as the neuropathological hallmark of PSP [28] (Fig. 1A). The atrophy of the midbrain with the preservation of the pons constitutes a specific pattern resembling a humming bird or a penguin and is known as the "humming bird sign" (HBS) [6,29], sometimes also called the "penguin silhouette sign", which are seen on midsagittal section [30] (Fig. 1B). According to the study of Massey et al. [31] the HBS has a very high specificity (100%) and PPV for a pathological diagnosis, but much lower sensitivity (68%). It is evidenced that smaller size of the midbrain area is associated with faster clinical progression [32]. To be more precise and objective linear or surface morphometric evaluations may be used. The midbrain atrophy can be assessed by measuring its anterior–posterior diameter on sagittal images (cut off value 11.6 mm) [28]. The midbrain area can also be measured in sagittal projection and the value ≤ 105 mm^2 indicates the diagnosis of PSP [33]. Oba et al. [30] suggest that value <70 mm^2 strongly indicates PSP. The latter parameter permits to discriminate between PSP and control patients with 100% of sensitivity, however specificity is lower due to the overlap with some MSA-Parkinsonism (MSA-P) patients [28].

The SCP (superior cerebellar peduncle) width is the next radiological parameter proved to be reduced in many studies [34] with the cut-off value ≤ 3.0 mm (measured on axial images) as proposed by Gama et al. [33] (Fig. 2A). It was observed that SCP width showed the largest reduction in the consecutive MRI examinations – performed within less than 2 years after initial MRI, which suggests its utility in monitoring the progression of the disease [34].

However, there is a lack of clear conclusions from studies how early in the disease course the MRI findings typical for PSP diagnosis occur, clinical experience and indirect data from recent studies suggest they are rather late. In the study of Kim et al. [35], MRI midbrain tegmentum diameter was shortened in PSP patients, but mean time from disease onset to MRI examination was 4.09 years.

In order to differentiate between PSP and MSA-P patients who share some of the radiological features, Quattrone et al. [36] proposed a combination of these measurements by counting MCP/SCP ratio (middle/superior cerebellar peduncle) and P/M ratio (pons/midbrain) (Fig. 2B). Since both SCP and M are reduced in PSP, these two values are higher among PSP patients in comparison to MSA-P or PD.

Another parameter which may help to distinguish the group of PSP patients is the higher MR parkinsonism index, which is calculated according to: $[(P/M) \times (MCP/SCP)]$. According to Quatrone MR parkinsonism index distinguishes patients with PSP from PD, MSA-P and healthy controls with 100% specificity and sensitivity and 100% of PPV. This parameter can be useful not only in the process of diagnosis, but it can also be a good marker of the disease progression [36].

In PSP the changes of signal in degenerated tissues, such as T2W hyperintensities in the tegmentum, tectum [37] and periaqueductal area [16] were also reported. In DWI MRI studies greater ADC values of the SCPs were evidenced in comparison to PD patients or healthy controls [38]. DTI studies revealed widespread white matter degeneration in PSP. Abnormalities were seen in the body of corpus callosum, cingulate gyrus, associative fibers: superior and inferior longitudinal fasciculi and SCPs – in which diffusion changes correlated strongly with clinical disease severity [39]. VBM MRI studies revealed the cortical atrophy in frontal and parietal lobes [40], precise manual measurements proved reductions also in the striatum – caudate nucleus and putamen [41].

The data on the utility of MRI in differentiation between PSP subtypes is very limited. Longoni et al. [42] showed a relatively smaller involvement of infratentorial brain in PSP-P compared
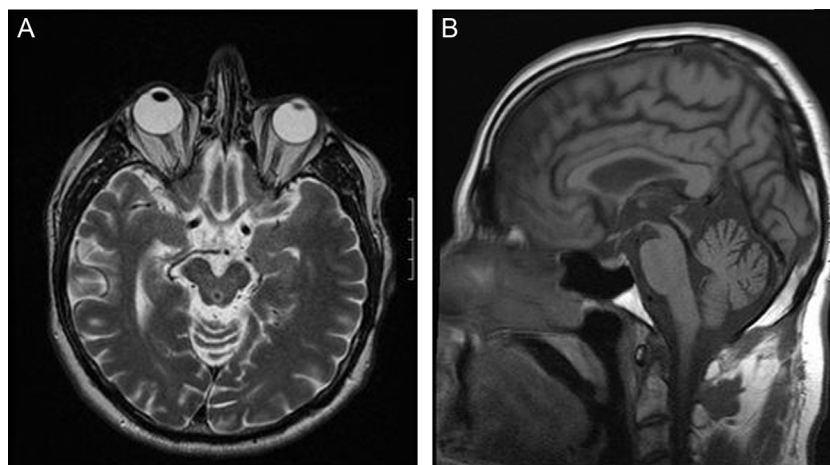

Fig. 1 – The atrophy of midbrain with the enlargement of the third ventricle and hyperintensities of signal in the periaqueductal area (A, axial T2W); "humming bird sign" in PSP patient (B, sagittal T1W).
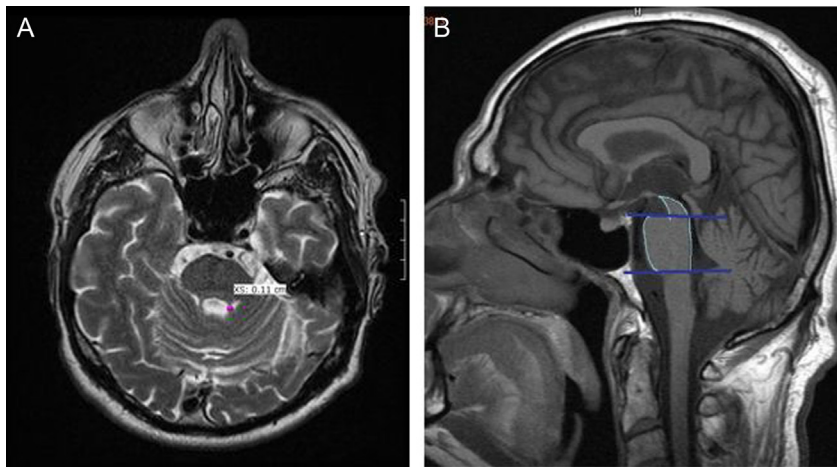
Fig. 2 – Measurements of SCP (superior cerebellar peduncle) (A, axial T2W); measurements of midbrain and pons area (B, sagittal T1W) in a PSP case.

to PSP-RS. This is in agreement with Whitwell's et al. [43] study, which showed that midbrain area is not reduced in PSP patients who have atypical clinical presentation. It indicates that midbrain atrophy can be a marker of RS but, on the other hand, the lack of its atrophy does not exclude a pathological diagnosis of PSP. These two studies have also found a correlation between subtle midbrain atrophy in PSP-PNFA, with subsequent symptoms of classic RS. It suggests that midbrain volume reduction can indicate probable future development of RS symptoms.

TCS is another non-invasive tool supportive for PSP diagnosis. It is recommended by EFNS for differential diagnosis of PD from APD and secondary parkinsonian syndromes [7]. The normoechogenicity of substantia nigra (SN) is a finding typical for PSP and MSA patients, whereas in PD SN is hyperechogenic [44,45], but lenticular nucleus (LN) hyperechogenicity is characteristic for PSP and MSA, but not PD patients. It was evidenced that marked, at least unilateral SN hyperechogenicity in combination with normal LN echogenicity differentiates PD from PSP and MSA patients with a PPV >90% [45,46]. TCS can also support the differentiation between PSP and CBD. In study of Walter's [47] the combination of marked SN hyperechogenicity and third-ventricle width <10 mm indicated CBD with a sensitivity of 83%, a specificity of 100%, and a PPV of 100%.

Functional neuroimaging techniques are also useful in PSP diagnosis. In many SPECT and FDG-PET studies hypoperfusion and hypometabolism in the frontal lobes (typically posterior) (Fig. 3), striatum, thalamus and midbrain [8] were observed in PSP patients.

FDG-PET study of Srulijes group evidenced the difference in metabolism between PSP-RS (pronounced frontal and thalamic hypometabolism) and PSP-P patients (pronounced putaminal hypometabolism) [48].

PET imaging with 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile [F-18] FDDNP probe, which enables the visualization of pathological hyperphosphorylated tau deposits in living brains, is another promising technique. This method detects tau aggregates in subcortical

and cortical areas with the pattern specific only to PSP, regardless of its clinical variability. Presumably, this technique may be helpful not only as a valuable diagnostic tool for all PSP phenotypes, but also in future as an indicator of treatment efficacy [49].

3.2. MSA

MSA is a member of the group of neurodegenerations called alpha-synucleinopathies. Its prevalence rates range between 1.9 and 4.9 per 100 000 [50]. The major neuropathology consists of degeneration of the nigrostriatal and olivopontocerebellar structures [5]. Clinically the disease is manifested by: parkinsonian syndrome, autonomic dysfunction (orthostatic hypotension, erectile dysfunction, urinary incontinence and constipation), and cerebellar signs [5]. According to the predominance of clinical features MSA consists of two forms: MSA-P – with predominant parkinsonism (80% of patients) and
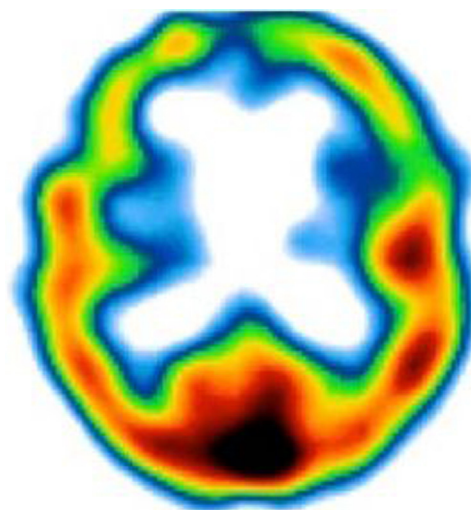

Fig. 3 – The rCBF SPECT examination of PSP patient showing hypoperfusion of frontal lobes.

MSA-C – with predominant cerebellar ataxia (20% of patients), accompanied by dysautonomia in both subtypes [51]. These two clinical variants also differ in terms of brain areas involved in the pathological process – in MSA-C neurodegeneration affects predominately brainstem and cerebellum and in MSA-P basal ganglia, particularly the putamen are involved [6,52].

Typical radiological features observed in MSA-P are: hyperintense putaminal rim, putaminal atrophy and hypointensity, atrophy and signal decrease of the globus pallidus and infratentorial signal increase and atrophy. The involvement of the infratentorial structures is more specific for MSA-C. In MSA-C the most characteristic changes are: atrophy of the middle cerebellar peduncle, the dilatation of 4th ventricle, atrophy of pons, increased signal within the cerebellum, middle cerebellar peduncles and pons [15,53]. However, it was documented that radiological findings considered to be more typical of MSA-P, such as putaminal atrophy, are also found in the clinical MSA-C cases and, conversely MSA-P patients may present cerebellar signs. It was proven that these cerebellar findings in MSA-P patients can still be highly specific for the diagnosis of MSA-P when compared to PD (90–100%), but are less sensitive (14–71%) [54]. The supratentorial abnormalities were observed more often and earlier in MSA-P and conversely the infratentorial appeared more often and earlier in MSA-C patients [55].

It is evidenced that both MSA phenotypes share the common pathological process, which explains the overlap of clinical symptoms and radiological signs between them. The atrophy of the putamen, middle cerebellar peduncle and pons or cerebellum in both MSA forms is enclosed in the revised diagnostic criteria of MSA [5].

T2-weighted hyperintensities may be helpful in making diagnosis. Savoiardo evidenced the presence of signal hyperintensities in the pons, middle cerebellar peduncles, and cerebellum among MSA patients [56]. The signal increase in MCPs was proven to be a useful parameter in diagnosing MSA-C with the high specificity (100%) and sensitivity (85.2%) in comparison to PD, PSP patients and controls [38,57]. The increased signal within the basis pontis, caused by the degeneration of the pontine neurons and transverse pontocerebellar fibers with the preservation of corticospinal tracts, forms a radiological hallmark for MSA called "hot-cross bun" (Fig. 4A). It can be seen on transverse T2W images of the brain as a cruciform hyperintensity in the pons [52]. The finding was reported to have a very high specificity and PPV (97%), but low sensitivity (50%) [15] in differentiating MSA from PD and PSP. Nevertheless, although the "hot cross bun" sign is typical, it is not pathognomonic to MSA [58]. The finding has also been observed in cases of spinocerebellar ataxia (SCA) types 2 and 3 and brainstem vasculitis [59]. The presence of a cruciform hyperintensity is correlated with the duration of the disease, which indicates that this sign may serve as a parameter for measuring the disease progression [59].

The common observation in MSA patients is the hypointensity of the basal ganglia on T2-weighted MRI images, frequently with lateral putaminal hyperintensivity, which reflects the degeneration of putamen [60–62]. It may be considered as another radiological sign of MSA called the "putaminal hyperintense rim" (HPR) (Fig. 4B–E). It was reported as having 100% specificity and positive predictive value in MSA-P versus PD and controls at 1.5 T [53]. Nevertheless, it should be mentioned here that at a high magnetic field strength the HPR sign is not an exclusive hallmark of MSA, but it is considered to be a normal finding in 3 T MRI in healthy subjects [60,63].

All these signal abnormalities generally become more pronounced with the disease's progression. In a longitudinal MRI study of Horimoto et al. [64] the pontine "hot cross bun" sign was completed mainly before 5 years from the symptoms onset in MSA-C patients, and even later in MSA-P. The HPR sign appeared as bilateral changes within 3–6 years in MSA-P cases, in MSA-C at least 4 years were required even for unilateral changes of signal to be detected [64].

Several histopathological studies revealed increased iron concentration in the putamen, which correlates with MRI findings in iron-sensitive sequences like $T2^*$-GRE [10], which allowed to differentiate MSA from PD patients accompanied with SWI technique, in which much higher iron deposition was observed in the putamen of MSA-P as compared to PD [13].

In everyday radiological practice some morphometric studies can also be easily conducted and used as supportive diagnostics of MSA, e.g. the measurement of the pons, whereby an area <315 mm^2 in the sagittal projection indicates its atrophy and the diagnosis of MSA-C with a positive predictive value of 72.7% [33].

The reduction of the MCP width may support the previous findings showing pontocerebellar atrophy as the pathological hallmark of the disease.

The average width of the MCP was significantly smaller in patients with MSA than in those with PD or control subjects. In accordance to Nicoletti et al. [65] the width of MCP is a parameter which helps to distinguish between patients with MSA from those with PD with a sensitivity of 100%, a specificity of 100%, and a positive predictive value of 100%. The proposed cut off value is ≤8 mm in the sagittal projection [65].

A significant difference in the average width of MCP was observed between the two groups: patients with "hot-cross bun sign" had the MCP width significantly smaller, which confirms a correlation between the presence of cruciform hyperintensity and severe atrophy of the MCP [65].

DWI MRI images revealed enhanced values of rADC coefficients in the putamen of the MSA-P patients in comparison to PD, which allows to differentiate these diseases [66]. Abnormal diffusity measures were also reported in MCP [65,67], cerebellum [67], pons [68]. A prospective study of Pellecchia et al. [69] revealed that abnormal diffusity in the putamen increased over time and can be a marker of the disease progression.

FDG-PET studies in MSA have shown decreased glucose metabolism in the putamen, brainstem and cerebellum and their results were incorporated into Gilman's MSA criteria [5].

The role of TCS in diagnosing MSA was discussed earlier.

3.3.   CBD

CBD is another, but less common and probably underdiagnosed taupathy [70,71]. The true incidence of the disease is unknown [72]. The pathological changes are localized predominantly in the frontoparietal cortex, basal ganglia and substantia nigra [70]. The disease presents usually with
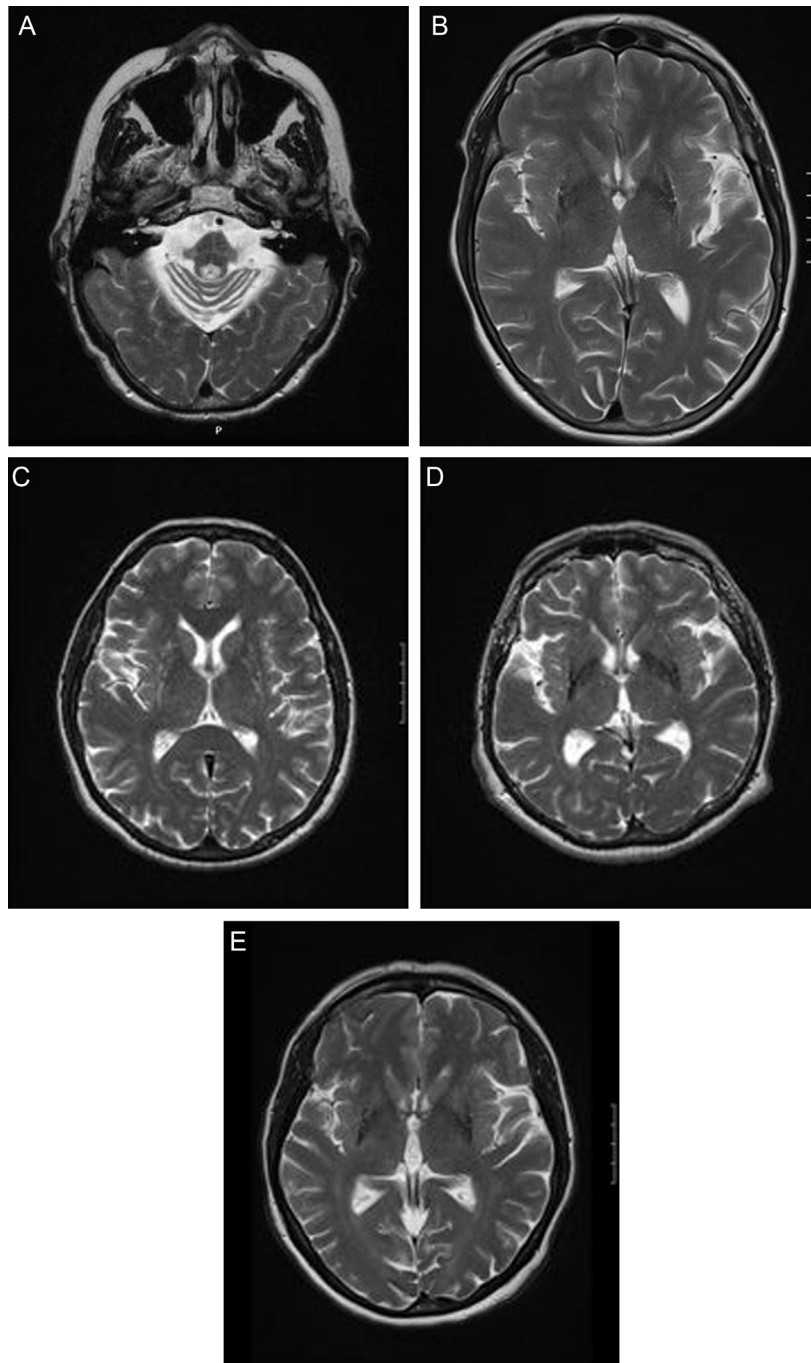
Fig. 4 – The ''hot cross-bun sign'' in MSA-C case (A, axial T2W); the images of putaminal hypointensity and ''slit-like'' marginal hyperintensities with ''hyperintense putaminal rim'' HPR sign (axial T2W) in 4 different MSA-P patients (B–E).

highly asymmetric symptoms with diverse clinical presentations which include both: cortical dysfunction (apraxia, 'alien limb' phenomena, cortical sensory loss, myoclonus, mirror movements, aphasia or hemispatial neglect) and basal ganglia dysfunction (bradykinesia, progressive asymmetric rigidity, dystonia, tremor) totally not levodopa responsive [73]. The clinical diagnosis of CBD is challenging due to its asymmetrical onset accompanied by upper limb apraxia, often misdiagnosed (limb-kinetic apraxia interpreted as bradykinesia) as PD. The typical clinical presentation of CBD may be presented by different underlying pathologies as Alzheimer's, PSP or even Creutzfeldt–Jakob disease. Therefore, recently the term corticobasal syndrome (CBS) has been proposed to cover the broad pathology comprising the clinical syndrome [74]. Obviously, it may complicate establishing a uniform neuroimaging pattern of this syndrome. Routine brain MRI usually shows asymmetric atrophy in the fronto-parietal regions and asymmetric enlargement of the lateral ventricles contralateral to the more affected side [75,76]. The T2-weighted MRI images of patients with CBD revealed significant signal hypointensity in the
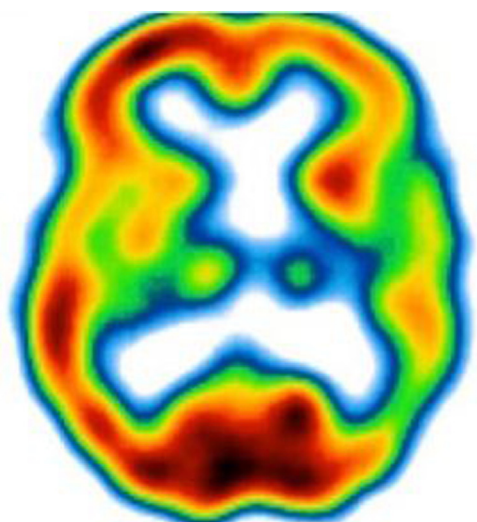
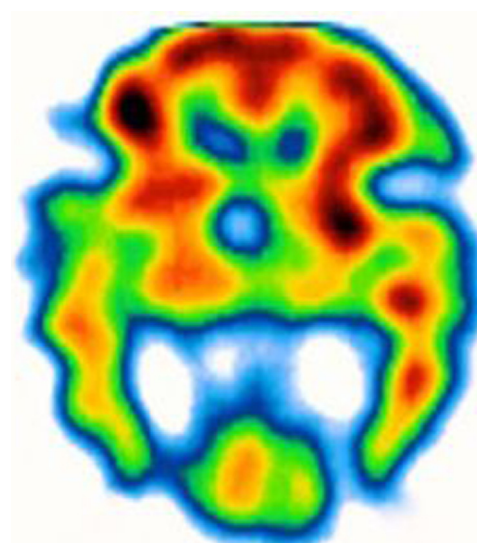**Fig. 5 – rCBF SPECT of CBS patient with unilateral, asymmetric hypoperfusion.**

Fig. 6 – rCBF SPECT of DLB patient showing the hypoperfusion of occipital lobes.

putamen and globus pallidus [77] and hyperintensive signal changes in the motor cortex or subcortical white matter [56,78]. On diffusion-weighted MRI images (DWI) a significant difference in rADC coefficients between extensive hyperintensity in the frontoparietal white matter can be observed, especially on the predominant side of cortical atrophy [38]. DTI studies revealed degeneration of motor pathways, especially the corticospinal tracts, which may explain the presence of pyramidal symptoms among some CBS patients [79]. Cortico-subcortical atrophy is contralateral to the side of the body most affected clinically, but at the early stages it may be not so evident and the early asymmetry may be better detected by rCBF SPECT (Fig. 5) or PET unilateral hypoperfusion [80].

3.4.   DLB

DLB is a synucleinopathy and the second most common disorder among neurodegenerative dementias after Alzheimer's disease (AD) [81]. The prevalence is estimated as 3.8–4.5% of all diagnosed dementias [82]. DLB is characterized by dementia with fluctuations of cognitive status, visual hallucinations and parkinsonian signs (bradykinesia, rigidity, tremor) [83], as well as hypersensitivity to neuroleptics [4], which occurs in 30–50% of patients [82].

The pathological process affects brain stem nuclei and many other areas, such as limbic and neocortical regions [4]. The disease clinically is often confused with other dementias, usually AD and PD. Although there are formal clinical criteria [4] the differentiation can be often difficult because of clinical overlaps between these disorders and potential difficulties to diagnose dementia preceding parkinsonism, which is the core feature of DLB. It has been shown that in MRI of DLB patients the mesial temporal lobe (especially the hippocampus) is relatively preserved in comparison to AD [84–87]. MRI VBM studies showed the significant involvement of subcortical regions with striatal and putaminal atrophy [84,88].

DLB diagnosis may be improved if supported by functional imaging as PET and SPECT [89]. In DLB the hypoperfusion of the occipital lobes have been reported in PET and SPECT studies [90,91] (Fig. 6). The real cause of this observation is not clear, what is more, the majority of VBM MRI analyses did not show any relation to the structural changes in occipital lobes [84,92].

4.   Conclusions

There has been a remarkable progress in the neuroimaging techniques in atypical parkinsonism in the recent years. Neuroimaging results can strongly support the clinical diagnosis which is crucial for the prospective care planning. Nevertheless, the increasing data on mixed pathologies and overlapping clinical presentations of those disorders (different presentations of PSP with classical Richardson syndrome in only 50% of cases or CBS covering wide spectrum of pathologies) makes the precise differentiation difficult (Table 1).

Furthermore, those radiological markers or hallmarks in many APD are usually rather late findings, so their utility for earlier diagnosis and possible medical interventions may be questionable. Those regarded as typical findings may be visible only with the use of special MRI sequences and the standardized protocols e.g. instituted by NNIPPS (Neuroprotection and Natural History in Parkinson's Plus Syndromes), which was intended to measure disease severity and progression in multicentre clinical trials (Table 2). The diagnosis of the APD can be improved both by applying new MRI techniques and modifying conventional sequences. The use of 3 or 7 T MRI scanners will probably strengthen the diagnostic value too, but they are not widely available and the use of 7 T is still controversial in humans [2]. Although there is a lack of effective treatments of APD, the biomarkers revealing subtle changes, which are able to predict the clinical diagnosis may be valuable in case of the availability of disease-modifying therapies.

Table 1 – Characteristic features of brain MRIs in Parkinsonian disorders (according to Sitburana and Mahlknecht) [40,93].								
	Atrophy of midbrain	Pons and cerebellum atrophy	Putaminal atrophy	Cortical atrophy	rADC↑	Special signs	Low values of M/P ratio	High values of MRPI
PD	+	−	+	+	−	−	−	+
PSP	+++	+	−	++	++putamen +++SCP	HBS	+++	+++
MSA-P	++	++	+++	+	+++putamen	PRH	+	−
MSA-C	+	+++	+	+	+	HCB sign	−	−
CBD	+	−	−	+++	−	Asymmetry	−	−
DLB	−	−	+	+	−	−	−	−

PD – Parkinson's disease; PSP – progressive supranuclear palsy; MSA-P – multiple system atrophy-parkinsonian type; MSA-C – multiple system atrophy-cerebellar type; CBD – corticobasal degeneration; DLB – dementia with Lewy bodies; rADC – regional apparent diffusion coefficient; HBS – ''hummingbird sign''; PRH – ''putaminal rim hyperintensity''; HCB – hot cross bun sign; SCP – superior cerebellar peduncles; M/P – midbrain/pons; MRPI – MR parkinsonism index [(P/M) × (MCP/SCP)]; MCP – middle cerebellar peduncles.

Table 2 – NNIPPS imaging protocol for Parkinson's plus syndromes according to Rolland et al. [27].								
Plane	Acquisition	Slice	Number of slices	Film[a]	TR (ms)	TE (ms)	FOV (mm)	Matrix
Sagittal	FGE T1 weighted	5	16	1	250–512	14–16	230–240	512 × (224–256)
Axial bicallosal plane	FSE proton density	3	40	2	5270–6000	12–20	230–240	256 × (224–256)
Axial bicallosal plane	FSE T2 weighted	3	40	2	5270–6000	75–110	230–240	256 × (224–256)
Coronal orthogonal to the bicallosal plane	FSE T2 weighted	3	40	2	4520–5200	96–110	230–240	512 × (204–256)
Axial[b]	3D IR T1 weighted	0.9	160	2[c]	2500IT = 500	Minimum	230–230	256 × 256

3D – three dimensional; FGE – fast gradient echo; FOV – field of view; FSE – fast spin echo; IR – inversion recovery; TE – echo time; TR – repetition time; NNIPPS – Neuroprotection and Natural History in Parkinson's Plus Syndromes.
[a] Printed films contain 20 images each.
[b] The whole cerebrum including the cerebellum and brainstem.
[c] Reconstruction of 20 slices at 5 mm thickness in the bicallosal plane, centered on the basal ganglia.

Conflict of interests

On behalf of all authors the corresponding author declares no conflict of interests.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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