Dyskinesia in Multiple System Atrophy and Progressive Supranuclear Palsy

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Abstract:

In the differential diagnosis of Parkinson syndromes, the response to L-Dopa is an essential criterion for the diagnosis of idiopathic Parkinson's disease (IPD), and the presence of L-Dopa-induced dyskinesia (LID) is considered a supportive criterion. This implies that in the presence of LID an atypical Parkinson-syndrome (APS) is unlikely. However, dyskinesia, and in particular LID, can also be present in APS such as MSA and PSP, although less frequently, and with varying clinical appearance. We conclude that whilst presence of dyskinesia provides support for a diagnosis of IPD, they do not allow reliable differentiation from APS.

Introduction

An important motor complication in the course of drug therapy of neurodegenerative parkinsonism is the occurrence of the so-called levodopa-induced dyskinesia (LID). LID are usually classified as peak-dose dyskinesia, wearing-off or off-period dyskinesia, and biphasic dyskinesia. In addition, dystonia in the absence of treatment may occur The exact causes of dyskinesia are not yet clarified. An essential prerequisite for the occurrence of LID is the response to levodopa. The main risk factor is long duration of treatment, but occasionally LID may be observed even after only a few days or months of treatment (Cilia 2014 Brain). In addition, young age of onset and high daily doses are considered major risk factors (Fahn 1999, Olanow 2013, Stocchi 2010). LID, or severe levodopa-induced chorea, are considered to be a supportive prospective positive criteria for PD (Gibb and Lees 1988) and their presence is often regarded as making an atypical Parkinson syndrome (APS) unlikely.

The topic of this workshop was to compile and discuss the evidence whether dyskinesia also occur in Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP), whether these differ from LID in PD, whether a response to levodopa is a prerequisite for the occurrence of the LID. We discussed current clinical practice and then re-evaluated the existing literature.

Pathophysiology of levodopa-induced dyskinesia (LID)

Dyskinesia or abnormal involuntary movements can be side effects of various medications, with levodopa (or dopamine agonists) most commonly being associated with dyskinesia in patients with Parkinson's disease (PD) or atypical Parkinson syndrome (APS). However, their pathophysiology is not well understood. Possible additional causes that have been considered are (i) non-physiological (pulsatile) dopamine replacement therapy, (ii) progressive degeneration of dopaminergic neurons, (iii) levodopa uptake and innervation of striatal neurons via non-dopaminergic (serotonergic) neurons, (iv) supersensitivity of dopamine D2 (-like) receptors (DRD2), (v) levodopa-induced synaptic plasticity of medium spiny GABAergic striatal projection neurons, and (vi) alterations of neuronal networks. Thus, LID in patients with PD are often attributed to pulsatile dopaminergic

stimulation together with the short half-life of levodopa and also the abnormal release of dopamine from serotonergic neurons (Nutt 2007, Politis 2014). Levodopa is therefore considered necessary but insufficient to generate LID since LID requires combinations of pulsatile delivery (short half-life), presynaptic nigrostriatal degeneration, metabolism of excess levodopa in serotonergic neurons, a relatively preserved post-synaptic nigrostriatal system and downstream changes of postsynaptic signaling molecules (Espay 2018).

The importance of pulsatile stimulation is supported by the fact that peak-dose dyskinesia increases in a dose-dependent manner with orally administered levodopa, whereas continuous levodopa infusion (levodopa carbidopa intestinal gel, LCIG) can reduce dyskinesia despite higher daily doses of levodopa (Olanow 2014). LID gradually emerges with oral therapy over time, i.e. the threshold for dyskinesia (which typically is initially higher than the threshold for a motor benefit) is lowered corresponding to a shift of the dose–response curve to the left, consistent with sensitization. However, motor fluctuations are complex with evidence for both sensitization and tolerance, depending upon what aspects of the motor response are examined (Mouradian 1988). Given that extracellular striatal dopamine concentrations are not constant in the normal brain, the pattern of variations in striatal dopamine concentrations in the conventionally levodopa–treated parkinsonian brain will not mimic the normal pattern (Nutt 2007). Uptake of levodopa into serotonergic neurons was initially suggested when an increase of LID was noticed after transplantation of fetal mesencephalic tissue. Subsequently, imaging studies confirmed that dopamine release from serotonergic neurons and its modulation via serotonin receptor activation (5HT1A) relate to LID (Politis 2014).

Changes within postsynaptic medium spiny neurons also appear to contribute to the pathophysiology. Dyskinesia can be caused not only by dopamine and dopamine agonists but also by dopamine receptor antagonists. Neuroleptic-induced dyskinesia and LID are similar in their clinical phenomenology, epidemiology, risk factors and pathophysiological mechanisms (Rascol and Fabre 2001; Sachdev 2000, Sawa and Snyder, 2002). Typical neuroleptics are selective antagonists at dopamine D2 (-like) receptors (DRD2), so that an increase in signaling through DRD2 is assumed to be relevant. Chronic inhibition of dopamine signaling along the nigrostriatal dopamine pathway can produce a compensatory upregulation in the striatal DRD2 level and increased coupling to the linked Gα protein (Cai et al., 2002), resulting in the

hypothesized increase in DRD2 signaling (Geurts 1999, Ginovart 1999). More specifically, Sanci and colleagues (Sanci 2002) and Drucker and colleagues (Drucker 1994) showed that neuroleptic treatment produces supersensitivity of striatal D2 but not D1 dopamine receptors. Loss of dopaminergic terminals as observed in PD also results in a compensatory DRD2 upregulation in early diseased patients (Antonini et al., 1994). On the other hand, levodopa treatment usually causes LID in patients with PD only following several years of disease (Marsden 1994), when DRD2 binding has returned to normal or subnormal values (Antonini 1997). Thus, additional changes downstream of DRD2 activation seem to be required to produce abnormal involuntary movements (AIMs).

Thus, neuroleptic-induced and also levodopa-induced dyskinesia have been linked to non-physiological DRD2 stimulation, resulting in altered expression of glutamate receptors and firing patterns of downstream nuclei within the basal ganglia loop. Temporal patterns of electrical activity are disrupted within the globus pallidus and the subthalamic nucleus in MPTP/levodopa treated monkeys (Vitek and Giroux, 2000). Molecular mechanisms have mainly been studied in rats. There is evidence for alterations of NMDA receptors: increased expression, hyperphosphorylation and abnormal trafficking (Dunah et al., 2000). These findings motivated experiments showing that blockade of NMDA receptors can reduce abnormal levodopa-induced behavior in monkeys (Blanchet 1998, Papa and Chase 1996). Since low-affinity glutamate receptor antagonists have been used to treat PD, these preclinical data were transferred to clinical studies: amantadine significantly reduced levodopa-induced AIM in patients with PD (Verhagen Metman 1998). At present, it is not clear how GPCRs (G-protein coupled receptor) such as dopamine receptors couple to ligand-gated ion channels such as NMDA or AMPA receptors. One may speculate that modulation of the activity of second and third messenger molecules such as kinases, etc. are involved. On the other hand, Niznik and coworkers described an intriguing model for direct blockade of NMDA receptors via the intracellular C-terminal tail of DRD1 following activation (Lee 2002). In addition, the coupling of dopamine receptors to G-proteins seems more complex since individual receptors can couple to different G proteins (Sidhu and Niznik 2000). However it seems likely that modulations of glutamate receptor expression represent molecular changes that occur several steps downstream of non-physiological DRD2 stimulation.

Beyond the similarities of dyskinesia induced by levodopa and neuroleptics converging on DRD2, overactivation of dopamine D1 (-like) receptors (DRD1) is associated with multiple molecular changes within striatal medium spiny neurons including activation of the mitogen and stress-activated kinase-1 which is regarded as a major factor in the regulation of synaptic plasticity and transcriptional activity (Calabresi 2010). Current concepts include abnormalities in non-dopaminergic neurotransmitters, i.e. the cholinergic, opioid, histaminic, adrenergic, glutamatergic, and cannabinoid systems (Espay 2018).

Furthermore changes in synaptic signaling leads to changes in neuronal networks. Data from animals and humans suggest that alterations in firing patterns in the globus pallidus pars interna and in the subthalamic nucleus secondary to overstimulation of dopamine receptors in the dysfunctional striatum are associated with LID (Espay 2018). Changes in the coherence between (motor) cortical structures and subcortical modulators seem to be a major factor in humans, including a reduction of power in the beta-band local field potential activity and narrowband hypersynchronous gamma oscillations in the motor cortex and the subthalamic nucleus with strong phase coherence between the two (perturbation in oscillatory dynamics) (Swann 2016), although the role of plastic alterations at the cortical level is still not well defined in this context, either in PD or in other neurodegenerative parkinsonism.

Neuropathological evidence

Dyskinesia is very rare in patients with PSP, and only few single pathological reports of patients with PSP and dyskinesia have been published. Except for a patient with additional Lewy bodies (overlap syndrome), no clear distinguishing pathological features have been described in these (Birdi 2002). In MSA, on the other hand, a substantial proportion of patients can experience dyskinesia, especially during the early stages of the disease. The underlying pathology for dyskinesia, which may occur even in untreated MSA, is thought to be related to putaminal degeneration, or degeneration of interconnections between the striatum and brainstem or cerebellum (Boesch et al, 2002). However, in a series of pathologically confirmed patients with MSA who underwent DBS surgery, of whom most experienced peak-dose dyskinesia, a typical distribution of pathological changes was seen in the striatum at postmortem (Meissner 2016). In the recent review of young-onset cases of MSA

(Batla et al, 2018), 56% had dyskinesia. Amongst those with pathologically confirmed young onset MSA 43% also had dyskinesia (compared to 94% in young-onset Parkinson's disease) and 29% had orofacial dyskinesia which was not recorded in any of the young-onset PD cases. Those with pathological confirmation were also found more likely to have the minimal-change pathological variant than those with late onset of the disease, with neuronal loss largely localized to the substantia nigra and the locus coeruleus (2 cases), while a further six had neuronal loss particularly in the striatonigral and olivopontocerebellar structures (three cases) and in the olivopontocerebellar structures (three cases). In an additional informative case report of a patient with pathologically confirmed young-onset MSA treated with DBS for severe dyskinesia there was also minimal-change pathological confirmation of MSA with significant cell loss restricted to the substantia nigra. Whilst there are therefore currently unequivocal data on the pathological substrate of the occurrence of dyskinesia in MSA, dyskinesia occur in the context of relatively preserved postsynaptic striatal neurons (Boesch 2002, Huang et al, 2005).

Clinical evidence for the presence of dyskinesia in MSA

Over the course of multiple system atrophy (MSA), various neuronal pathways are affected by a neurodegeneration. This results in a multifaceted clinical presentation with parkinsonism, cerebellar ataxia, and autonomic failure in variable combinations (Wenning et al., 2013; Low et al., 2015; Krismer and Wenning, 2017). Two major motor presentations can be distinguished. MSA parkinsonism (MSA-P) is the MSA form that predominates in Western countries and is characterized by a rapidly progressive akinetic-rigid syndrome with a poor response to treatment with levodopa due to striatal neurodegeneration (Krismer and Wenning, 2017). Disease progression is faster than in PD and postural instability and falls emerge already within the first three years of disease onset (Williams and Litvan, 2013). The cerebellar type (MSA-C) shows prominent cerebellar symptoms including gait and limb ataxia, scanning dysarthria as well as oculomotor disturbances such as gaze-evoked nystagmus and hypometric saccades (Krismer and Wenning, 2017). By definition, all MSA patients exhibit pronounced autonomic dysfunction, affecting urogenital and cardiovascular autonomic domains (Gilman et al., 2008). Human neuropathological examinations have revealed that the primarily affected cell populations are oligodendrocytes which

harbor alpha-synuclein immunopositive inclusions (Trojanowski et al., 2007). In addition, prominent neuronal loss and astrogliosis are present (Koga and Dickson, 2018). It is assumed that there is a propagation mechanism for alpha-synuclein that is responsible for the disease spread in MSA resulting in neurodegeneration in many different brain regions (Krismer and Wenning 2017, Wenning 2018).

Dyskinesia in MSA is observed almost exclusively in the MSA-P subtype where parkinsonism is often treated with dopaminergic therapies but classically responds poorly. However, levodopa therapy causes complications such as motor fluctuations in MSA as well. These dyskinesia typically have a craniocervical predominance and are mostly dystonic (Boesch 2002). However, these are not exclusive since peak dose dyskinesia occur and may be associated with slower progression (Berciano 2002, O'Sullivan S 2008). Williams and Litvan locate MSA dyskinesia primarily to the axial segment (Williams and Litvan 2013), whereas Espay and coworkers locatetypical MSA dyskinesia more to the feet (Espay 2018).

In a prospective European MSA cohort study, 141 patients were closely followed of whom 62% were classified as MSA-P and 38% as having MSA-C. A beneficial response to levodopa was reported in 43% of MSA-P and in 13% of MSA-C patients, lasting for a mean duration of three to four years. Of all these patients a minority encountered motor complications including wearing-off fluctuations in 23%, off-dystonia in 20%, on-off motor fluctuations in 14%, but peak-dose dyskinesia were reported only in 11% of levodopa-responsive patients (Wenning 2013). Similar observations were found in the corresponding prospective US MSA cohort study (Low 2015).
A recent analysis of young-onset MSA patients with an age of less than 40 years included 22 patients (20 MSA-P and 2 MSA-C type) (Batla 2018). The mean age at MSA onset was 36.7 years. In comparison to young-onset PD, LID were less common in MSA patients but orofacial dystonia in response to levodopa was only seen in young-onset MSA but not in young-onset PD. However, if the young-onset MSA patients were compared to late-onset MSA patients from the above mentioned European MSA cohort, dystonia, levodopa responsiveness but also levodopa-induced dyskinesia, were more common in young patients. In detail, 83% of young-onset MSA subjects had an initial response to levodopa and 44% developed limb

and/or orofacial dyskinesia (Batla 2018). A rather high prevalence of dyskinesia was again found in four out of five late-onset cases from a retrospective study in neuropathologically confirmed MSA-P patients which had been initially diagnosed as PD and had received deep brain stimulation (Meissner 2016).

These data suggest that the occurrence of dyskinesia is not a reliable distinguishing feature of PD and MSA, as dyskinesia can occur to a considerable degree as levodopa-induced motor complications in MSA patients, especially in the MSA-P type and in early-onset MSA patients. However, orofacial distribution and off-period and wearing-off dystonia are more common in MSA. In particular, the occurrence of dyskinesia resp. dystonia of the oromandibular region and of the platysma suggest MSA in the differential diagnosis.

Clinical evidence for the presence of dyskinesia in PSP

Progressive supranuclear palsy (PSP) is pathologically characterized by cerebral intracellular tau aggregation which leads to neurodegeneration (Frosch, 2017). The clinical spectrum of neuropathologically defined PSP is broad and can show an overlap with autopsy-confirmed MSA, PD, and frontotemporal dementia (FTD) (Respondek and Höglinger, 2016), which has led to novel criteria for the clinical diagnosis of PSP (Höglinger 2017). As shown in PD for alpha-synuclein, tau is also thought to spread transneuronally in a prion-like manner (Lim and Yue 2015, Mudher 2017) and it is suggested that different PSP phenotypes might be related to differential seeding and spreading properties of distinct tau strains (Narasimhan 2017).
Clinically, poor response to dopaminergic drugs is one diagnostic criterion suggested to be useful in distinguishing APS from PD (Suchowersky 2006). Thus "poor or absent response of parkinsonism" to LD is supportive of PSP diagnosis while marked and prolonged LD benefit has been included as a mandatory exclusion criterion for PSP (Litvan 2003).
Dyskinesia in PSP patients is "rare" (Litvan 1996, Lang 2005), and LID is typically not observed in PSP (Respondek and Hoglinger 2016), but there is lack of systematic study data. LID in PD is linked to responsiveness to levodopa and based on a relatively preserved post-synaptic nigrostriatal system (Espay 2018). In contrast to

PD, PSP patients with the most common Richardson phenotype (PSP-RS) usually do not respond to levodopa, and the post-synaptic dopaminergic system is also affected in these patients (Williams and Litvan 2013). In accordance, Lang suggested that in PSP patients, "the usual absence of dyskinesias as a side effect, even with high doses of levodopa, probably relates to the prominent pathological involvement of the internal segment of the globus pallidus, essentially resulting in an ´autopallidotomy´" (Lang, 2005).

However, patients with PSP-Parkinson (PSP-P) phenotype who represent about 20-32% of PSP patients, often show a moderate initial response to LD and because they frequently present with concomitant asymmetric parkinsonism and tremor, they are clinically often indistinguishable from PD in the first years of disease (Williams 2005, Levin 2016).

Constantinescu et al. reviewed eight publications with in total about 228 medicated PSP patients and reported at least some LD response in 26% to 38% of these patients within the first year of illness (Constantinescu et al., 2007). Considering the studies reviewed (Nieforth and Golbe 1993, Williams 2005, Kompoliti 1998) and a recent investigation (Vasta 2017), the degree of LD response varies from minimal/very low to marked/good (Kompoliti 1998, Nieforth and Golbe 1993, Vasta 2017, Williams 2005). However, included PSP patients have not been classified into clinical subtypes. Dyskinesia have been reported in about ten of the 228 PSP patients from the review (Constantinescu 2007), suggesting a prevalence rate of about 4.4%, but PSP was proven by autopsy in only seven of these ten patients. When separating the 228 PSP patients into two groups, one with 95 patients in the largest study by Williams and coworkers (Williams 2005) and one with 133 patients in the remaining seven studies, the prevalences of dyskinesia match quite well with 4.0% in the study by Williams et al. and about 4.5% in the remaining 7 reports. There is a further single-case report describing LID in an autopsy-proven case of PSP (Kim 2002). Studies in PSP patients aiming to systematically report or investigate dyskinesa are lacking. Like in PD, dyskinesia found in PSP patients usually was based on at least some LD-responsiveness and were related to LD therapy. However, "some (PSP) patients with dyskinesia may obtain little or no clinical benefit otherwise" (Lang 2005). Birdi et al. even described blepharospasm and intermittently occurring facial dyskinesia in two drug-naïve PSP patients. Facial dyskinesia

presented as tonic contraction or grimacing of one or the other side and they worsened on dopaminergic treatment (Birdi 2002).

Dyskinesia in PSP patients has been described in most cases only to be facial and, when more detail was given, as occurring as LID with jaw clenching, retraction of the mouth angles or as intermittent unilateral tonic facial muscle contractions or blepharospasm (Birdi 2002). However, LID of the limbs have been reported in two cases, presenting as choreatic dyskinesia in combination with blepharospasm in one case (Birdi 2002), in the other case as LD-dose dependent occurring in one leg with semirhythmic flexion-extension of the left knee and internal rotation as well as adduction of the hip joint (Kim 2002). Noteworthy, one patient with limb dyskinesia had combined Lewy body and PSP pathology (Birdi 2002).

Further clinic-pathological studies should investigate whether dyskinesia in PSP is linked to certain clinical or pathological phenotypes, such as overlap syndromes of tau- and alpha-synucleinopathy or with underlying genetic overlap of PSP and PD with MAPT H1-specific polymorphisms or genetic forms with rare variants in the LRRK2 gene as found in autopsy-proven PSP, respectively (Respondek 2018).

Discussion

In summary, there is ample clinical and pathological evidence for the occurrence of LID in parkinsonian disorders other than PD, e.g. MSA or PSP. However, several points need to be considered:

1) Diagnostic certainty: the rate of misdiagnosis of patients at lifetime is known to be high. Thus, patients with PD may be diagnosed with PSP or MSA and LID are actually observed as part of misdiagnosed PD.

2) Phenotypical heterogeneity: dyskinesia in MSA and PSP patients may differ from the ones observed in PD and the terminology used may be ambiguous (including distribution, timing and differentiation of treatment-induced vs spontaneous dyskinesia).

3) Pathological heterogeneity: disease progression on the histological level is not uniform in all PD patients (Rietdijk 2017), and not all patients with PD develop dyskinesia. Heterogeneity of disease spread and thus heterogeneity of affected brain regions are also likely to exist in MSA and PSP, opening the possibility of relative post-synaptic preservation, which then can predispose to LID, similar to PD.

4) Underdosage: LID is evoked by pulsatile dopaminergic stimulation and in most cases requires high doses of levodopa. Many patients with MSA or PSP do not receive high doses of levodopa, because the drug has been discontinued due to insufficient clinical effects or unwanted side-effects. In contrast, almost all patients with PD receive dopaminergic medication and at some point progress to higher levodopa doses, thus increasing the likelihood for LID. Therefore, although some patients with APS could be more prone to develop LID, they may fail to develop LID due to limited dopaminergic stimulation.

There are ongoing efforts to improve the subtyping of parkinsonian syndromes using a combination of clinical features, MRI or PET imaging and molecular biomarkers (e.g. Fereshtehnejad 2017, Zhang 2019). These analyses may also help to identify subgroups within disease entities, such as MSA or PSP, that are predisposed to the development of dyskinesia and yield further explanation on why some patients are more prone than others to develop dyskinesia in the course of their disease.

Conclusion

Based on the evidence available, we thus suggest:

-       Dyskinesia, and especially LID can also occur in atypical parkinsonian syndromes, such as MSA or PSP, albeit less frequently than in PD.

-       The clinical picture of dyskinesia in MSA and PSP may differ from dyskinesia in PD (e.g. more frequent oromandibular or axial distribution), but the clinical heterogeneity does not permit using the phenomenology as a reliable factor differentiating between disease entities.

-       There is currently a lack of adequate epidemiological data on dyskinesia in APS as well as clinical classifications.

-       Therefore, the presence or absence of dyskinesia does not reliably differentiate between IPS and APS

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