How to approach a patient with parkinsonism — red flags for atypical parkinsonism

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Abstract

Parkinsonism is a clinical syndrome defined by bradykinesia plus rigidity or tremor. Though most commonly encountered in the setting of idiopathic Parkinson's disease, a number of neurodegenerative, structural, metabolic and toxic neurological disorders can result in parkinsonism. Accurately diagnosing the underlying cause of parkinsonism is of both therapeutic and prognostic relevance, especially as we enter the era of disease-modifying treatment trials for neurodegenerative disorders. Being aware of the wide array of potential causes of parkinsonism is of paramount importance for clinicians. In this chapter, we present a pragmatic clinical approach to patients with parkinsonism, specifically focusing on 'red flags', which should alert one to consider diagnoses other than idiopathic Parkinson's disease.

1. Introduction

First clearly defined by Jean Martin Charcot during his leçons du Mardi (Tuesday lessons), Parkinsonism is a clinical syndrome characterized by three cardinal motor manifestations: bradykinesia, rigidity and tremor (Goetz, 1986; Postuma et al., 2015). Of those, bradykinesia must be present

to diagnose parkinsonism and it should be accompanied by either tremor or rigidity (or both). Its pathophysiologic basis remains incompletely understood, but parkinsonism is increasingly being viewed as a network disorder (Caligiore et al., 2016), whereby dysfunction in any number of functionally interconnected brain regions can potentially produce the syndrome (Joutsa, Horn, Hsu, & Fox, 2018). Conceptualizing parkinsonism as a network disorder helps to understand why its presence is common to such a great variety of otherwise apparently pathophysiologically unrelated disorders.

Parkinsonism remains a purely clinical diagnosis, and while most patients with parkinsonism will turn out to have idiopathic Parkinson's disease (PD), being cognisant of, and probing for alternative explanations is of clinical and prognostic importance. Indeed, a variety of degenerative and non-degenerative, hereditary and acquired disorders can lead to parkinsonism. Differentiating these from PD can at times be challenging. Awareness of the broad range of causes of parkinsonism, and of signs incompatible with PD are important tools for the clinician. Here, we provide a systematic, structured approach to the assessment of patients with parkinsonism, emphasizing in particular 'red flags' and clinical clues, which may suggest a diagnosis other than idiopathic PD.

2. Parkinson's disease-what is 'normal'?

Idiopathic Parkinson's disease (PD) is the commonest cause of parkinsonism worldwide, and by far the most likely diagnosis in a patient presenting with parkinsonsim. A definite PD diagnosis still remains possible only at post-mortem, and in the absence of high-fidelity biomarkers, misdiagnosis still occurs. The job of the movement disorder neurologist is therefore to identify those cases where the clinical syndrome appears incongruent with this diagnosis, and to pursue further testing accordingly. The first step in this quest is to define what is 'normal' or 'typical' for PD. This can be complicated given the large phenotypic variability that has been described within PD itself.

PD classically begins around the age of 60–65 years, and is slightly more common in men (De Lau & Breteler, 2006; Alves, Forsaa, Pedersen, Gjerstad, & Larsen, 2008). The disease generally starts insidiously and has an asymmetric onset. Motor symptoms, consisting of bradykinesia, rigidity and tremor are generally preceded (often for many years) by a variety of non-motor manifestations (REM sleep behavior disorder, apathy,

depression, anosmia, constipation)(Massano & Bhatia, 2012). Tremor is classically present at rest, 4–6 Hz in frequency, "pill-rolling" in nature and suppressed by voluntary movement, only to later 're-emerge' if posture is maintained (Postuma et al., 2015). Tremor in other locations including the chin, jaw and tongue (but not the head) may be seen (Massano & Bhatia, 2012). Rigidity refers to 'lead-pipe' resistance felt throughout the range of movement, to which superimposed tremor may be appreciated as 'cog-wheeling' (Postuma et al., 2015). Bradykinesia can be seen using a number of examination techniques, including finger/foot tapping, pronation/supination hand movements and importantly must comprise both slowness and decrement in speed/amplitude (Postuma et al., 2015).

Patients classically walk with a forwardly stooped (camptocormic) posture, often with reduced arm-swing (worse on the more affected side) and taking short shuffling steps (festination), but with a narrow base. Turning may be difficult, and performed 'en-bloc', while freezing of gait may be observed, particularly when negotiating thresholds or in confined spaces. Abnormalities on 'pull-testing', indicating postural instability, emerge as the disease progresses. Other neurological features including oculomotor abnormalities, cerebellar dysfunction, pyramidal signs, peripheral neuropathy and cognitive dysfunction (early in the disease course) are unusual (Massano & Bhatia, 2012).

Structural brain imaging is typically normal (Mahlknecht et al., 2010; Pagano, Niccolini, & Politis, 2016). Dopamine transporter (DAT) SPECT imaging reveals asymmetric, bilateral reduction in striatal uptake, more marked in the posterior putamen (generally worse contralateral to the clinically more affected side) (Pagano et al., 2016).

3. Where to begin?

The approach to a patient with parkinsonism should always begin with a thorough history. This should specifically focus on the time-course of the illness, pattern and tempo of progression, as well as the presence of both motor and non-motor manifestations. 'Red-flags', as set out in a number of diagnostic criteria, should be systematically sought (Gibb & Lees, 1988; Hughes, Daniel, Kilford, & Lees, 1992; Postuma et al., 2015). Past medical history and current and prior medication use is important to assess, especially if considering the possibility of drug-induced

parkinsonism. Exposure to nigral toxins is important to identify e.g. pesticide exposure in farmers, as is occupational history e.g. manganese exposure in welders (Lev, Melamed, & Offen, 2007). Family history should be scrutinized, both to enable targeted genetic testing in cases of familial parkinsonism, and to avoid pitfalls in diagnosis (familial MSA for example is vanishingly rare)(Gilman et al., 2008). Questioning should not be limited to family history of parkinsonism, but should include family members affected by gait imbalance, tremor, cognitive dysfunction, psychiatric disease and other abnormal movements. Inquiring about both upstream and downstream generations is necessary, particularly in disorders showing anticipation and in patients with Fragile X tremor ataxia syndrome (FXTAS), who may have grandchildren manifesting Fragile X mental retardation syndrome. Ethnic origin and ancestry are also important to ascertain-*LRRK2* gene mutations for example are more common in the Ashkenazi Jewish population (Alcalay et al., 2014), MSA-Cerebellar (MSA-C) is more common that its parkinsonian counterpart in Japan (the opposite is true in Caucasians), while junctophilin-3 mutations causing HDL-2 are generally only encountered in individuals of African descent (Im, Kim, & Kim, 2015; Anderson et al., 2017).

Following a thorough history, the next step in the evaluation of patient with parkinsonism involves a complete neurological examination. The aim of this exercise is two-fold. First, to confirm the presence of bradykinesia and at least one other motor manifestation, thereby confirming the presence of parkinsonism; second, to systematically examine the patient for features which would be incongruent with a diagnosis of PD.

Structural neuroimaging should be performed in all cases to assess for causes of secondary parkinsonism (structural lesions, normal pressure hydrocephalus), to assess the burden of vascular disease (especially in cases of lower body parkinsonism) and to evaluate for the presence of imaging feature suggestive of atypical parkinsonian syndromes. Additionally, DAT SPECT imaging, which can assess the integrity of nigrostriatal dopaminergic projections with a high degree of fidelity, is useful in cases with diagnostic uncertainty, in order to confirm the presence of neurodegeneration (Tolosa, Borght, Moreno, & DaTSCAN Clinically Uncertain Parkinsonian Syndromes Study Group, 2007; Seifert & Wiener, 2013).

While the discussion above has outlined the approach to making a diagnosis of PD, what is equally important is to recognize what features suggest an alternative cause for parkinsonism, what that cause might be, and how to

pursue appropriate lines of investigation. In this regard, we find a number of clinical clues particularly useful. Many of these form part of the 'red flags' or 'exclusion criteria' of existing diagnostic schema (Hughes, Daniel et al., 1992; Postuma et al., 2015). Others are appreciated after many years of clinical experience. We discuss a number of these below, though this should by no means be regarded as an exhaustive list.

4. Clinical clues within the motor parkinsonian syndrome

4.1 Postural stability and gait

Postural instability and falls are a feature common to most parkinsonian syndromes, where they have a significant impact on quality of life and predict shorter survival (Bloem, Hausdorff, Visser, & Giladi, 2004). Timing of falls relative to disease onset can be a useful diagnostic clue in the evaluation of patients with parkinsonism. In particular, early postural instability with falls, especially within the first two years of a parkinsonian syndrome is highly atypical in PD and should heighten suspicion for PSP. Williams et al. retrospectively examined timing and predictors of falls in neuropathologically-confirmed parkinsonian syndromes (Williams, Watt, & Lees, 2006) and found that the median time to first fall was shortest in patients with PSP-RS (12 months), intermediate in patients with MSA and PSP-P (42 and 47 months respectively) and longest in patients with PD (108 months).

Inquiring about falls, and when they first occurred is therefore a high-yield question in patients with parkinsonism.

Gait characteristics are also useful to assess. In PSP, patients often walk with an upright posture (as opposed to camptocormic PD patients) and the gait frequently has a 'veering' or 'lurching' quality, described by some as a 'drunken sailor gait' (Morris, Wood, & Lees, 1999; Burn & Lees, 2007; McFarland & Hess, 2017). Patients' loss of insight into their postural instability may lead them to walk in a reckless fashion, turning with apparent disregards for their falls risk and briskly rising from a chair -the so-called "rocket sign".

A broad-based, ataxic gait with inability to tandem walk on the other hand should raise suspicion for MSA, spinocerebellar ataxias and Fragile X-associated tremor/ataxia syndrome (Park, Kim, & Jeon, 2015; Jacquemont et al., 2003).

4.2 Distribution of parkinsonism

Lower body parkinsonism describes a predominant affectation of lower limbs, producing disproportionate gait difficulty with festination, freezing, turning difficulty and postural instability in the setting of relatively preserved (though often also involved) upper limb function.

The presence of lower body parkinsonism should make one consider two principal differential diagnoses-vascular parkinsonism, and normal pressure hydropcephalus (NPH)- though idiopathic PD as well as PSP and CBS can have gait-predominant initial manifestations which may be confused with lower body parkinsonism (Höglinger et al., 2017; Sakamoto, Shimizu, Tobisawa, & Isozaki, 2017).

In such cases, specific questioning about the presence of vascular risk factors (VP), cognitive decline and urinary symptoms (NPH) as well as brain imaging help to narrow the differential diagnosis.

4.3 Tremor

Paying careful attention to the characteristics of the tremor can provide useful diagnostic clues. In PSP, tremor is typically absent. If present, it is typically mild, often postural, and rarely pill-rolling in character (Fujioka et al., 2016), although patients with PSP-P may present with rest-tremor resembling PD. In MSA, the classic 'pill-rolling' PD rest tremor is also unusual. Rather, MSA patients tend to exhibit a small amplitude, jerky postural tremor which, if observed carefully is actually myoclonic in nature. This polyminimyoclonus, may be stimulus sensitive. Intention tremor may also be seen, particularly in MSA-C, and also in FXTAS (Gilman et al., 1998 and 2008; Hagerman & Hagerman, 2015; Jacquemont et al., 2003). Tremor in CBS, if present, is generally jerky in nature (myoclonus), and accompanied by other signs including cortical sensory loss, apraxia, dystonia and rigidity in the affected limb (Stover, Walker, & Watts, 2007).

4.4 Bradykinesia

In contrast to classic, progressively decrementing bradykinesia, patients with PSP may exhibit a particular type of rapid finger tapping abnormality, termed hypokinesia without decrement (finger tapping being fast, but of small amplitude from the beginning of the motion, rather than decrementing) (Morris et al., 1999; Ling, Massey, Lees, Brown, & Day, 2012).

4.5 Rigidity

Velocity-dependent increases in tone (spasticity), are not a feature of PD. Their presence should alert the clinician to one of the pallido-pyramidal syndromes (see below), or to CBS, especially if markedly asymmetric.

5. Other clinical clues from the neurological examination

5.1 Examination of the eyes

Examining the eyes is of significant diagnostic value in cases of undifferentiated parkinsonism. In PD, eye movements should be full in range with normal saccadic latency, speed and accuracy. As PD generally affects an older population however, one should bear in mind that some changes in ocular motility (e.g. restriction in up-gaze) can be seen as part of normal aging. A number of features on eye examination may suggest a diagnosis other than PD. These include:

5.1.1 Eye movements examination

Cerebellar eye signs such as square wave jerks, saccadic dysmetria and nystagmus are incongruent with a diagnosis of idiopathic PD. MSA should be high on the list, especially if autonomic disturbances are present (Quinn, 1989; Palma, Norcliffe-Kaufmann, & Kaufmann, 2018). The spinocerebellar ataxias (most commonly SCA2, 3, 6 and 17) should also be considered, as these may produce parkinsonism in addition to cerebellar signs and gait ataxia (Park et al., 2015; Latorre et al., 2019; Chen et al., 2005). Slow horizontal saccades (especially in SCA2), a dominant family history of gait ataxia or parkinsonism and cerebellar atrophy on structural brain imaging may further support this diagnosis. Square wave jerks are commonly seen in PSP, but other cerebellar eye signs are not typical (Chen et al., 2010).

Supranuclear Gaze Palsy describes a difficulty in initiating voluntary eye movements due to dysfunction in supranuclear control of communication to cranial nerve nuclei. Reflex eye movements, assessed through the doll's eye maneuvers, are preserved. Both vertical and horizontal supranuclear gaze palsies are important to assess in the presence of parkinsonism.

Vertical supranuclear gaze palsy is a classic finding in PSP. It may however be absent early in the disease course, or incomplete, manifesting either as slowing of vertical saccade or the so-called 'round-the-houses' sign, where the eyes do not move directly vertically but rather in a lateral arc, when

asked to perform direct vertical saccades. Non-specific visual symptoms are common in early PSP, due to fixation instability or disrupted saccade control mechanisms, and may be present prior to the emergence of overt clinical signs (Morris et al., 1999). VSGP can be seen in other parkinsonian disorders including PD, CBS, MSA and FXTAS (Martin, Hartlein, Racette, Cairns, & Perlmutter, 2017; Fraint et al., 2014). Parkinsonism alongside VSGP in young individuals should make the clinician consider both Kufor Rakeb syndrome (KRS) and Niemann Pick type C (NPC). In this setting, searching for other clinical clues such as pyramidal signs, cognitive decline and facial-finger-faucial mini myoclonus (KRS) and ataxia, seizures and gelastic cataplexy (NPC) becomes important (Williams, Hadeed, al-Din, Wreikat, & Lees, 2005).

Horizontal supranuclear gaze palsy has received less attention but is equally important to assess. Indeed abnormalities of horizontal gaze are found particularly in Gaucher disease, which is (as well as GBA heterozygous states) a risk factor for development of Parkinson's disease (Accardo, Pensiero, Ciana, Parentin, & Bembi, 2010; Koens et al., 2018).

Apraxia of saccade initiation, manifesting as an increased latency to saccade commencement, most pronounced ipsilateral to the side exhibiting apraxia is a classic finding in corticobasal syndrome (Armstrong, 2016). Difficulty initiating voluntary saccades, as well as fixation difficulties (the eyes frequently being drawn to new visual stimuli in the visual periphery) are also a common finding in HD (Lasker & Zee, 1997), where anti-saccades may be particularly impaired (Lasker & Zee, 1997).

5.1.2 Other eye- and eyelid abnormalities

Eyelid opening apraxia is a debilitating condition characterized by an inability to voluntarily open the eyes without visible contraction of the orbicularis oculi muscle (in contrast to blepharospasm). This classic feature of PSP may be triggered in the clinic by asking the patient to forcibly close the eyes and then try to open them. The condition is actually a result of dystonic contractions of the pre-tarsal portion of the orbicularis oculi muscle, and as such, is often helped by pre-tarsal botulinum toxin injections (Piccione, Mancini, Tonin, & Bizzarini, 1997).

Kayser-Fleischer rings, resulting from excess copper deposition on the inner surface of the cornea are the ophthalmological hallmark of Wilson's disease. Seen as a golden, brown ring in the peripheral cornea, this finding should be sought in all cases of Parkinsonism (it is present in nearly all cases of neurological Wilson's disease) (Czlonkowska et al., 2018). Its identification

can be difficult, especially early in the disease or with darkly pigmented irizes, hence slit lamp examination may be necessary to make the diagnosis.

Eyelid ptosis can be a feature of a number of neurological conditions, but in the parkinsonian realm in particular, should raise suspicion for a mitochondrial disorder. Indeed, a number of mitochondrial disorders, especially POLG1-related disorders, can manifest with parkinsonism, usually of the atypical variety (Miguel et al., 2014; Orsucci, Ienco, Mancuso, & Siciliano, 2011). In this setting, other features of mitochondrial disease including ophthalmoplegia, deafness, short stature, seizures and systemic organ dysfunction (diabetes mellitus, cytopaenias) should be sought (Miguel et al., 2014; Orsucci et al., 2011).

Examination of the lens is also important. *Sunflower cataracts* are another characteristic finding in Wilson's disease (Czlonkowska et al., 2018). Moreover, early cataracts may be a clue to some rarer disorders mimicking atypical parkinsonism, including cerebrotendinous xanthomatosis (cataracts-often juvenile- and chronic diarrhea are often present prior to neurological manifestations) (Monson et al., 2011) and mitochondrial disease.

5.2 Early cognitive and neuropsychiatric dysfunction

Though many patients with PD experience deficits in cognitive performance, especially with progression of their illness, the presence of significant cognitive impairment at the time of diagnosis is unusual (Roheger, Kalbe, & Liepelt-Scarfone, 2018), and should make one consider other disorders. Dementia with Lewy bodies (DLBs) is the second most common neurodegenerative dementia after Alzheimer disease, accounting for 5%–25% of all dementias (Boot, McDade, McGinnis, & Boeve, 2013; McKeith et al., 1996). Mean age of onset is generally around 75 years, with the condition being more common in males (McKeith et al., 1996). Alongside cognitive deficits, which are usually pronounced in the attention, executive function and visuospatial domains, at least one of the three core features of the condition (parkinsonism, visual hallucinations and fluctuations) must be present to make the diagnosis. *Parkinsonism* in DLB is little different from that of classic PD, but on average, there tends to be a prominence of axial symptoms, gait impairment, postural instability and relatively less tremor. Response to levodopa also tends to be poorer than in classic PD (McKeith et al., 1996). *Visual hallucinations* are usually complex and formed, typically taking the form of people, animals or mis-perceptions of normal visual stimuli e.g. faces emerging from patterns on chair cushions. *Fluctuations* manifest as periods of significant cognitive dysfunction alternating with periods of

near-normal function (Ferman et al., 2004). Profound fluctuations in alertness may also be present, manifesting as excessive daytime sleepiness, "going blank" or "switching off". *REM sleep behavior disorder, neuroleptic sensitivity,* (McKeith, Fairbairn, Perry, Thompson, & Perry, 1992), *autonomic dysfunction, which* can be pronounced, and abnormal DAT SPECT imaging-helps differentiation from AD (Piggott et al., 1999).

With regard to further dementias, parkinsonism is a well recognized manifestation of Alzheimer disease (AD). Its prevalence increases with disease duration, probably to around 30% (and in some series up to 60%) in moderately advanced AD (Lopez, Wisnieski, Becker, Boiler, & DeKosky, 1997; Pearce, 1974). Bradykinesia and rigidity are the most common motor symptoms, with tremor being relatively rare (Lopez et al. 1997; Pearce, 1974). Hughes et al. retrospectively examined neuropathologic findings in 100 patients clinically diagnosed by neurologists as having idiopathic PD; misdiagnosis rate was 24%, with Alzheimer pathology being the most common mimic (alongside PSP pathology)(Hughes, Daniel, et al., 1992). The development of parkinsonian symptoms in AD is a predictor of institutionalization, and probably correlates with both a lower baseline cognitive performance, and faster progression of cognitive decline (Lopez et al. 1997; Wilson et al., 2000). Such an association may reflect global progression of neurodegeneration in AD concurrently affecting both neocortical and basal ganglia structures, or perhaps progressive dopaminergic depletion worsens cognitive performance (Wilson et al., 2000).

Cognitive impairment affects the majority of patients with PSP at an early stage of the disease course. The pattern of cognitive impairment is generally classified as subcortical, typified by cognitive slowing, inefficient memory recall and executive dysfunction (as opposed to true amnesia which is more characteristically seen in conditions such as AD)(Gerstenecker et al., 2012; Kobylecki et al., 2015). In addition, behavioral symptoms tend to be prominent in PSP, being present along a spectrum ranging from mild emotional blunting, lack of insight and inappropriate social conduct to classic behavioral variant frontotemporal dementia (bvFTD)(Höglinger et al., 2017). In fact, 20%−30% of patients with PSP may initially manifest with a cognitive or behavioral syndrome, mimicking bvFTD (Höglinger et al., 2017; Kaat et al., 2007; Kobylecki et al., 2015) Significant apathy is often a prominent feature (Litvan, Mega, Cummings, & Fairbanks, 1996).

Psychiatric manifestations may be the presenting feature of *Wilson's disease* in up to a third of individuals (Czlonkowska et al., 2018). This may manifest during early schooling as impulsiveness, inappropriate behavior

or declining academic performance (European Association For The Study Of The Liver, 2012), or with a variety of mood and anxiety disorders throughout life. Neuropsychiatric symptoms (along with cognitive decline) are also a common finding in patients with *Huntington's disease*, and these are frequently present at pre-manifest stages. Apathy is the commonest behavioral feature, followed by depression (Naarding, Kremer, & Zitman, 2001; Teixeira, de Souza, Rocha, Furr-Stimming, & Lauterbach, 2016; Litwin et al., 2018). Schizophrenia-like psychosis are a rare presenting feature in HD, but may affect up to a third of individuals at some point in the disease course, more commonly at later stages (Naarding et al., 2001; Teixeira et al., 2016). Moreover, drug induced parkinsonism, 22q11.2 microdeletion syndrome (22q11.2 DS) and many other conditions may come into the differential diagnosis (Bassett & Chow, 2008; Boot et al., 2018; Schneider et al., 2014).

5.3 Presence of additional movement disorders

Parkinson's disease is generally a 'pure' hypokinetic movement disorder, and the presence of additional abnormal movements should alert the physician to the possibility of an alternative diagnosis. One important exception to this statement is that of dystonia (especially foot dystonia), which can be an initial manifestation of Parkinson's disease (particularly in young-onset and genetic forms) (Khan et al., 2003). Certain clinical syndromes in particular should raise eyebrows:

5.3.1 Dystonia

Dystonic phenomena are decidedly uncommon in patients with idiopathic PD, with the exception of foot dystonia and off-period dystonia in the setting of levodopa therapy. In contrast, dystonia is common in atypical parkinsonian disorders, and adopts distinct phenotypes in each condition, providing valuable clinical clues.

Severe anterocollis is a characteristic dystonia seen in patients with MSA (Quinn, 2005). In addition however, patients with MSA may exhibit more focal dystonia involving a single limb, or indeed manifesting initially as writer's cramp. Dystonic movements affecting the craniocervical and facial musculature induced by treatment with levodopa is a classic features of MSA (Boesch, Wenning, Ransmayr, & Poewe, 2002; Godeiro-Junior et al., 2008). Axial dystonic lateral trunk flexion, referred to as Pisa syndrome, may also be observed in MSA (Slawek et al., 2006). Pisa syndrome

is rarely encountered in PD, though it may be seen following dopaminergic (especially dopamine agonist) therapy (Galati, Möller, & Städler, 2014).

In contrast to the anterocollis seen in MSA, 'axial dystonia in extension' is the classically described dystonic manifestation of PSP (Steele, Richardson, & Olszewski, 1964). This refers to the tonic, rigid nuchal and trunk extension seen in the condition, though some authors have suggested that describing this phenomenon as dystonia represents a misnomer, owing to the fixed neck position and absence of sensory gestes which typify primary dystonias (Barclay & Lang, 1997). As previously mentioned, blepharospasm and eyelid opening apraxia are also common dystonic features in PSP (Piccione et al., 1997).

Dystonic affectation of a limb is a particularly common finding in corticobasal syndrome. As with the other features of the disorder, it tends to be strikingly asymmetric, usually involving one arm and accompanied by apraxia, myoclonus and other cortical signs (Vanek & Jankovic, 2000; Stamelou, Alonso-Canovas, & Bhatia, 2012).

Jaw opening dystonia particularly if worsened by eating ('eating dystonia') carries a limited differential diagnosis. Panthotenate kinase associated neurodegeneration (PKAN), neuroferritinopathy and neuroacanthocytic disorders are the primary culprits, all of which may also manifest parkinsonism. The presence of this distinct syndrome should therefore engender a thorough search for these conditions, including blood film for acanthotytes and iron-sensitive brain MRI sequences looking for characteristic deposition patterns.

5.3.2 Myoclonus

A small amplitude myoclonic finger tremor ('polyminimyoclonus') is typical of MSA. Limb myoclonus (often stimulus sensitive) in the setting of markedly asymmetric parkinsonism should raise concern for CBS (Armstrong et al., 2013; Armstrong, 2014). Myoclonic jerks in a patient with a rapidly progressive cognitive syndrome accompanied by parkinsonism suggests prion disease (Maltête, Guyant-Maréchal, Mihout, & Hannequin, 2006). A particular type of myoclonus, termed facial-faucial-finger myoclonus is seen in KRS.

5.3.3 Chorea

In levodopa-naïve patients with parkinsonism, the presence of chorea almost always indicates a diagnosis other than idiopathic Parkinson's disease. The principal differential diagnoses to consider in this setting are Huntington's

disease (HD)/HD phenocopy syndromes and some of the NBIAs. In levodopa treated patients however, peak-dose and bi-phasic dyskinesia frequently manifest with choreiform movements.

Parkinsonism is a recognized feature of both adult and juvenile HD. In adult cases, it generally becomes prominent in the late stages of the disorder, when patients develop a more akinetic-rigid clinical phenotype. However, levodopa-responsive parkinsonism as a presenting feature of adult HD is described (Reuter et al., 2000), with some cases having reduced striatal DAT uptake, adding further diagnostic confusion with PD (Gamez et al., 2010). In juvenile HD (Westphal variant), akinetic-rigid parkinsonism is a typical feature, usually accompanied by dystonia (Roos, 2010). Parkinsonsim can also form part of the HDL-2 (junctophilin-3 mutations, the commonest HD mimic in South African populations) (Anderson et al., 2017), HDL-3 and HDL-4 (SCA 17) clinical syndromes, as well as that of other HD phenocopies (Park et al., 2015).

5.4 Pyramidal signs

Overt evidence of pyramidal dysfunction (pathologically brisk reflexes, spastic catch, sustained clonus, up-going plantar responses etc.) is distinctly unusual in Parkinson's disease. While some genetic forms of the disorder e.g. *Parkin* mutation carriers, may exhibit brisk reflexes as part of the syndrome, pyramidal signs should always lead the clinician to consider alternative diagnoses (Khan et al., 2003). Co-existent structural or degenerative spinal pathology should be excluded, especially given that PD affects an elderly population. Equally, significant intracranial vascular disease may explain pyramidal signs in patients with otherwise typical PD.

Within the realm of atypical parkinsonism, patients with MSA often exhibit brisk reflexes, though sustained clonus and/or spasticity would be unusual (Quinn, 2005). Equally in corticobasal syndrome, brisk reflexes and spasticity may be seen, particularly in the most affected limb.

Numerous other disorders, collectively termed pallido-pyramidal syndromes can produce the combination of parkinsonism and pyramidal signs, and these always warrant consideration in this scenario. Pallido-pyramidal syndromes have been extensively reviewed elsewhere (Tranchant, Koob, & Anheim, 2017), but a few disorders are worthy of particular mention here:

5.4.1 Complex hereditary spastic paraplegias

The hereditary spastic paraplegias are a heterogeneous groups of inherited neurological disorders characterized by progressive lower limb weakness,

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spasticity, hypertonic urinary bladder disturbance and often mildly impaired lower limb vibration sense. They can be 'pure', where the above features are the sole manifestations, or 'complex', where the syndrome also encompasses other neurologic disturbances such as ataxia, seizures, cognitive dysfunction, peripheral neuropathy or parkinsonism (Hedera, 2018).

Two recessively inherited complex HSPs, namely HSP11 and HSP 15, characteristically produce parkinsonism. Both generally manifest between the ages of 10 and 35 years with spastic paraplegia, cognitive decline, axonal motor neuropathy and parkinsonism (which may be levodopa responsive) (Tranchant et al., 2017). Characteristic neuroimaging findings include thinning of the corpus callosum (particularly in its anterior portion) and white matter hyperintensities adjacent to the frontal horns of the lateral ventricles-the 'ears of the lynx' sign (Mulroy et al., 2019). Parkinsonism has also rarely been reported as a feature of SPG 10 (Goizet et al., 2009).

5.4.2 Neurodegeneration with brain iron accumulation syndromes (NBIAs)

Panthotenate kinase associated neurodegeneration (PKAN) and PLA2G6 associated neurodegeneration (PLAN) are the two most commonly encountered NBIAs in clinical practice, and both frequently cause parkinsonism.

Young-onset 'typical' *PKAN* classically manifests with a dystonic phenotype with bulbar involvement and truncal opisthotonus alongside spasticity and visual impairment from retinal degeneration (Gregory, Polster, & Hayflick, 2009). Later onset 'atypical' PKAN often produces mixed dystonia/parkinsonism with early speech and/or bulbar involvement. Jaw opening/eating dystonia, pronounced pyramidal signs and neuropsychiatric symptoms are important clinical clues (Gregory et al., 2009; Hogarth, 2015). The 'eye of the tiger' sign, a classic PKAN imaging finding depicting a T2 hyperintense area within the globus pallidus surrounded by T2 hypointensity, is neither completely sensitive nor specific for the disorder (Hogarth, 2015).

PLAN was first recognized as causing a global neurodevelopmental regression syndrome termed infantile neuroaxonal dystrophy (INAD). In the last decade, an adult-onset form has been recognized. This synucleinopathy generally presents with early-onset dystonia/parkinsonism, pyramidal signs, ataxia and variable degrees of cognitive decline (Gregory et al., 2009). Dystonic opisthotonus, autonomic dysfunction, cerebellar atrophy and pallidal iron accumulation on MRI are important pointers to the diagnosis (Gregory et al., 2009; Hogarth, 2015). Importantly, iron accumulation

may be absent in *PLAN*, especially early in the disease course, despite significant clinical abnormalities (Hogarth, 2015).

Kufor Rakeb syndrome (PARK9) is a rare, recessively inherited parkinsonian syndrome first identified in a Jordanian family from the Kufor-Rakeb region, which also falls under the rubric of NBIAs. It usually manifests with early-onset levodopa responsive parkinsonism accompanied by cognitive decline, vertical supranuclear gaze palsy and pyramidal signs. Other features may include facial-faucial-finger mini-myoclonus and oculogyric dystonic spasms (Williams et al., 2005).

Most of the other NBIAs can also produce combined parkinsonism and pyramidal signs, alongside other syndrome-specific manifestations e.g. motor neuronopathy in mitochondrial membrane protein associated neurodegeneration (MPAN; may cause diagnostic confusion with amyotrophic lateral sclerosis) and neurodevelopmental regression with a Rett-syndrome phenotype in beta propeller protein associated neurodegeneration (BPAN).

- *FBXO7 gene mutation (PARK15)* generally manifests with early-onset levodopa responsive parkinsonism accompanied by pronounced pyramidal signs, psychiatric disturbances and oculomotor abnormalities including vertical supranuclear gaze palsy and oculomotor apraxia.

5.5 Voice and laryngeal function

Speech difficulties are common to a number of the parkinsonian disorders. The quality of voice alterations can sometimes provide clues as to the underlying condition. While speech in PD tends to have a hypophonic quality, the voice in PSP classically described as 'growling' dysarthria, which may be accompanied by constant groaning (Stamelou, Rubio-Agusti, Quinn, & Bhatia, 2011). In addition, patients with PSP may exhibit significant language difficulties (Burrell, Ballard, Halliday, & Hodges, 2018).

This is in contrast to the high-pitched, squeaky and at times broken quality of the voice in MSA (where cerebellar dysarthria may also be seen) (Quinn, 2005).

Nocturnal stridor is a potentially fatal (risk of sudden death) clinical finding which is relatively specific to MSA; it may be improved by nocturnal CPAP (Vetrugno et al., 2004).

Dysarthria, dysphagia (often with drooling) and risus sardonicus are also typical of Wilson's disease, and significant bulbar dysfunction is common in a number of NBIAs (Czlonkowska et al., 2018).

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6. Levodopa response and therapy-related effects

Only 75% of patients diagnosed during life as having Parkinson's disease will have this confirmed at autopsy (Hughes, Ben-Shlomo, Daniel, & Lees, 1992). Especially in the early stages of illness, differentiating PD from other disorders with similar symptomatology (in particular atypical parkinsonism) can be challenging. Excellent and sustained response to L-dopa therapy is a key supportive feature in the diagnosis of PD according to the Queen Square Brain Bank and MDS clinical diagnostic criteria, though objectively assessing levodopa response is more challenging than it may seem (Hughes, Daniel et al., 1992; Postuma et al., 2015).

The L-dopa challenge test has been developed as an objective means of quantifying motor improvement following administration of dopaminergic therapy, and is widely employed as a diagnostic and research tool. It involves rating motor features of disease, according to part III (motor) of the Unified Parkinson's Disease Rating Scale (UPDRS), before and after administration of a supra-threshold dose (often 250 mg) of L-dopa. When administered to patients with undifferentiated parkinsonian disorders, a greater improvement in motor function is observed in those patients who will eventually prove to be idiopathic Parkinson's disease (PD), as opposed to other parkinsonian syndromes (MSA, corticobasal syndrome, vascular parkinsonism etc.) (Schade et al., 2017). However, it is well recognized that parkinsonian syndromes other than PD may significantly improve with dopaminergic medication (Albanese et al., 2001; Hughes, Colosimo, Kleedorfer, Daniel, & Lees, 1992).

The utility of the L-dopa challenge test in predicting an eventual neuropathological diagnosis of PD is limited by poor positive and negative predictive values (Schade et al., 2017). In addition, the exact threshold defining improvement has not been clearly specified, though an improvement of at least 30% from baseline is generally accepted as representing a good response (Albanese et al., 2001; Gilman et al., 1998).

Aside from motor improvement, the presence and nature of treatment-related side-effects can be very informative. In particular, the emergence of dyskinesia and on-off motor fluctuations support a diagnosis of PD. Treatment-related motor complications can occur (albeit rarely) in non-genetic atypical parkinsonian syndromes such as PSP and MSA, but in this setting they usually adopt syndrome-specific characteristics. In MSA, levodopa-induced dyskinesia almost exclusively occurs in the parkinsonian subtype

(MSA-P), generally assume a dystonic quality and involve the facial or craniocervical region. Levodopa-induced facial pulling, risus sardonicus or dystonic head rotation should therefore alert clinicians to this diagnosis (Jost et al., 2019). Dyskinesia in PSP is vanishingly rare, but when it has been described, generally comprised jaw clenching and/or face pulling (Jost et al., 2019).

7. Rapidly progressive course

Parkinson's disease is generally insidious in onset with pre-clinical/prodromal phases lasting many years, followed by progressive motor disturbance, again, progressing over decades. A rapidly progressive clinical course (over days, weeks or months) should be a red flag for the presence of other conditions, particularly autoimmune, paraneoplastic and prion disease.

7.1 Paraneoplastic parkinsonism

Parkinsonism secondary to anti-neuronal antibodies rarely occurs in isolation; rather it is usually part and parcel of a complex neurological syndrome. Commonly implicated antibodies include anti-Ma2 (generally a PSP phenotype combined with other features of brainstem encephalitis), anti-Ri and anti-CRMP5 antibodies (both the latter usually also producing a complex encephalopathy) (Balint, Vincent, Meinck, Irani, & Bhatia, 2018). A small number of antibodies have been reported to cause parkinsonism-predominant paraneoplastic striatal encephalitis, though these represent less than 1% of all paraneoplastic neurological syndromes (PNSs) (Tada et al., 2016). The main culprit is the anti-CRMP5 antibody, though associations with other antibodies have also been documented, and a significant proportion remain seronegative (Honnorat & Antoine, 2007; Tada et al., 2016; Oguma et al., 2001). Aside from parkinsonism, patients with anti-CRMP5 PNS may exhibit encephalomyelitis, chorea, sensory neuronopathy, cerebellar syndromes, chronic gastrointestinal pseudo-obstruction and limbic encephalitis (Graus et al., 2004). The most commonly associated cancers are small cell lung cancer and thymoma (Graus et al., 2004).

7.2 Non-paraneoplastic antibody mediated parkinsonism

Within this realm, the principal disorder to consider is *anti-IGLON5 disease*, which is characterized by significant sleep abnormalities (REM and non-REM sleep parasomnias), bulbar dysfunction, ataxia, cognitive decline and

dysautonomia (Heidbreder & Philipp, 2018). PSP-like parkinsonism with akinetic-rigidity, gait imbalance and bulbar dysfunction is well recognized (Heidbreder & Philipp, 2018). The disease progresses slowly, with decades often elapsing between diagnosis and death. Neuropathology demonstrates a brainstem-predominant tauopathy, raising many interesting questions about the link between autoimmunity and neurodegeneration (Heidbreder & Philipp, 2018). Other antibodies to consider include LGI1, DPPX and GAD (in adults) and anti-D2R and anti-NMDA (in children) (Balint et al., 2018).

7.3 Prion disease

Akinetic-rigid parkinsonism/akinetic mutism is a classic features of end-stage Creutzfeld-Jakob disease. Atypical parkinsonism can however also be the presenting features of this progressive neurodegenerative disorder.

PSP-like (especially in the genetic prion disorder Gerstmann-Straussler-Scheinker syndrome-which can produce a parkinsonian syndrome evolving over years) and CBS-like (particularly alien limb phenomena) presentations of prion disease have clearly been described (Geschwind, 2015; Fleming, Ghetti, & Murrell, 2010; Maltête et al., 2006; Rowe et al., 2007).

In addition to rapid progression, cognitive decline and generalized myoclonus are important clinical pointers. Classic MRI (cortical diffusion restriction, pulvinar sign) and biochemical (elevated cerebrospinal fluid protein 14-3-3 and real-time quaking-induced conversion (RT-QuIC)) abnormalities may be absent in some genetic prion diseases (Green, 2019; Takada et al., 2017).

8. Diurnal fluctuations

Treatment-related motor fluctuations are commonly encountered in PD, both as wearing off phenomena (tremor, slowness of movement and anxiety) and ON-period dyskinesia. The emergence of such motor fluctuations generally occurs after a number of years of levodopa therapy, and their presence is highly unusual within the first 12 months of disease (Kikuchi, 2007). The presence of significant fluctuations in motor symptoms at the time of presentation, without dopaminergic treatment should prompt consideration of other disorders however, including dopa-responsive dystonia and genetically-mediated PD. Dopa responsive dystonia (DRD) is a collective term given to a clinically and genetically heterogeneous group

of disorders which typically manifest with early-onset dystonia with diurnal fluctuations, and demonstrate excellent and sustained response to levodopa therapy (Wijemanne & Jankovic, 2015). The most common and well-characterized disorder producing DRD is autosomal dominant GTP-cyclohydrolase-1 deficiency, though deficiencies in other enzymes involved in the dopamine synthesis pathway (e.g. tyrosine hydroxylase (TH), sepiapterin reductase (SR)), as well as other genetic disorders (hereditary spastic paraplegia type 11, SCA3, ataxia telangiectasia) can produce a DRD phenotype (Charlesworth et al., 2013; Wijemanne, Shulman, Jimenez-Shahed, Curry, & Jankovic, 2015; Wilder-Smith et al., 2003). Though most commonly producing a dystonic phenotype, DRD can manifest with parkinsonism which may be clinically indistinguishable from idiopathic PD. In the case of GCH1 deficiency, this is especially prevalent with individuals manifesting after the age of 15 years (Wijemanne & Jankovic, 2015). GCH1 deficiency may also represent a risk factor for the later degenerative parkinsonism (Mencacci et al., 2014). TH and SR deficiencies (usually recessively inherited) often produce much more complex phenotypes comprising encephalopathy, autonomic dysfunction, ptosis, hypotonia and delayed motor development (Wijemanne & Jankovic, 2015). Parkinsonism can form part of the clinical picture in both disorders. Oculogyric crises are an important clinical clue, though more common in SR (Wijemanne & Jankovic, 2015).

9. Systemic signs and symptoms

9.1 Liver disease

The presence of liver dysfunction alongside parkinsonism is an important finding which always deserves attention. The primary disorder which should be considered in this setting is *Wilson's disease*. Hepatic dysfunction is the earliest and most common manifestation (Schilsky, 2014), with neurological symptoms typically occurring later. The youngest reported case of neurological Wilson's disease is 6 years, but symptoms may first manifest in old age, even into the 8th decade (European Association For The Study Of The Liver, 2012). Neurological manifestations generally fall under three major categories: tremor, dystonia and parkinsonism. Parkinsonism is usually symmetric, and of the akinetic-rigid variety. Additional suggestive features include the classic 'wing-beating' tremor, cerebellar ataxia, swallowing difficulty with drooling, and dysarthria (which is itself the most common

neurological symptom in Wilson's disease, being present in up to 97% of cases), Kayser-Fleischer rings and Sunflower cataracts.

Hepatocellular dysfunction and porto-systemic shunting from any cause may also impair the usual hepatobiliary excretion of manganese (Rose et al., 1999). The resulting 'acquired hepatolenticular degeneration' or 'cirrhosis-related parkinsonism', seen in up to 20% of patients with moderate-to-severe cirrhosis (Burkhard, Delavelle, Du Pasquier, & Spahr, 2003), usually manifests with both akinetic-rigid parkinsonism and dystonia. Elevated serum manganese levels alongside pallidal T1 hyperintensity on brain MRI support the diagnosis, and should be sought in this particular clinical setting.

9.2 Organomegaly

The presence of hepatosplenomegaly should make one consider a diagnosis of Gaucher disease. Other features of this lysosomal storage disorder, which confers increased risk for PD, include cytopenia, bone pain and growth delay (Riboldi & Di Fonzo, 2019).

10. Clues from brain imaging

Structural neuroimaging using MRI is part of the routine evaluation of parkinsonian syndromes. While usually normal in PD, its utility lies in its ability to identify structural changes suggestive of atypical parkinsonian syndromes, as well as other neuroimaging features suggesting alternative diagnoses (including structural pathology, vascular lesions, normal pressure hydrocephalus and abnormal brain mineralization). DAT SPECT imaging is sometimes employed when there is doubt about the presence of nigrostriatal degeneration-though results can be mis-leading.

10.1 Progressive supranuclear palsy

The hallmark neuroimaging feature of PSP is that of striking midbrain atrophy. Described as the 'hummingbird' sign when viewed in the sagittal plane or as the 'mickey mouse' sign on axial brain imaging, this finding may be absent early in the disease, and is less pronounced in variant presentation of PSP (those other than Richardson syndrome) (Mulroy et al., 2019; Whitwell et al., 2017). Midbrain atrophy correlates well with the presence of the Richardson clinical syndrome, but does not predict the presence of PSP pathology (Whitwell et al., 2013). Another characteristic imaging

feature of PSP is marked atrophy of the superior cerebellar peduncles with relative sparing of the middle cerebellar peduncles (Paviour, Price, Stevens, Lees, & Fox, 2005).

10.2 Multiple system atrophy

In clinical practice, two characteristic features on structural brain imaging may suggest a diagnosis of MSA, though neither is completely sensitive or specific. The first is putaminal atrophy, occasionally accompanied by T2-weighted 'slit-like' hyperintensity around the putaminal margins (Brooks, Seppi, & Neuroimaging Working Group on MSA, 2009). The second is the 'hot-cross-bun sign', denoting a cruciform hyperintensity in the pons on axial T2-weighted imaging, which while often touted as characteristic of MSA, is present in some spinocerebellar ataxias and rarely in other disorders (Bürk, Skalej, & Dichgans, 2001). Atrophy of the cerebellum, pons, middle cerebellar peduncles as well as middle cerebellar peduncle hyperintensity and may also be seen.

10.3 Corticobasal syndrome

Structural neuroimaging in CBS generally shows asymmetric frontoparietal atrophy, most marked contralaterally to the clinically affected side (Whitwell et al., 2010).

10.4 Normal pressure hydrocephalus

Normal pressure hydrocephalus (NPH) is a poorly understood syndrome characterized by the triad of gait, cognitive and urinary symptoms in the setting of intracranial ventricular enlargement with normal CSF pressure (Molde, Söderström, & Laurell, 2017). The disorder bears characteristic neuroimaging findings, including ventricular enlargement disproportionate to cerebral atrophy without evidence of obstruction to cerebrospinal fluid flow, callosal angle less than 90°, periventricular hyperintensities (possibly reflecting transependymal oedema), tight sulci at the vertex and enlargement of the Sylvian fissures (Damasceno, 2015). Approximately 70% of patients with NPH exhibit parkinsonism. This is classically described (as in VP) as 'lower body parkinsonism', though in fact more than half exhibit upper extremity bradykinesia also (Krauss et al., 1997; Molde et al., 2017). Mechanical distortion of brain parenchyma, alterations in cerebral blood flow (including to basal ganglia structures) and increased periventricular water content have all been suggested as possible pathomechanisms (Owler et al., 2004). Diagnosis relies on identifying classic neuroradiologic

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appearances in typical (albeit sometimes incomplete) clinical syndromes; the CSF tap test (removal of 40–50 mL of CSF) or extended lumbar drainage procedures can further support the diagnosis and predict response to shunting (Damasceno, 2009; Wikkelsø, Andersson, Blomstrand, Lindqvist, & Svendsen, 1986).

10.5 Vascular parkinsonism

Vascular parkinsonism (VP) describes parkinsonian disorders temporally related or associated with ischaemic cerebrovascular events (Mostile, Nicoletti, & Zappia, 2018). It classically manifests with symmetric, lower body-predominant parkinsonism accompanied by gait imbalance, festination and freezing, generally without tremor. Pyramidal signs, pseudobulbar palsy, urinary incontinence and cognitive impairment are other recognized features (Winikates & Jankovic, 1999). Proposed pathomechanisms include ischaemic basal ganglia or subcortical white matter lesions, causing disruption in both structural and functional connectivity. MRI findings in the syndrome are poorly defined, but ischaemic sub-cortical leucoariosis and a degree of ventricular enlargement can be seen (Winikates & Jankovic, 1999). Significant vascular risk factors should alert the clinician to this possibility, especially in the presence of lower limb predominant symptoms.

10.6 Hereditary diffuse leucoencephalopathy with axonal spheroids

This disorder, caused by dominantly-inherited mutations in the CSF1R gene, commonly manifests with parkinsonism alongside cognitive decline and variable pyramidal signs (Sundal et al., 2013). Mean age of onset is around 45 years, and most patients die within a decade of onset. Frontal-predominant, non-enhancing deep periventricular white matter lesions are typical (Sundal et al., 2013).

10.7 Brain iron accumulation syndromes

The neurodegeneration with brain iron accumulation (NBIA) syndromes are a heterogeneous group of progressive neurodegenerative disorders which have in common the abnormal deposition of iron within basal ganglia (and often other central nervous system) structures. Symptoms common to many of these disorders include dystonia, spasticity, parkinsonism, cognitive decline and retinal degeneration, though both the age of onset, clinical syndromes, and degree of brain iron deposition remains highly variable, both

within individual disorders and between different NBIAs (Gregory & Hayflick, 2014).

Iron-sensitive MRI sequences (SWI, T2*, gradient echo) can be helpful, alongside clinical symptomatology, in identifying disease-specific signatures for distinct NBIAs (Schipper, 2012). Importantly, other disorders such as Parkinson's disease, Alzheimer disease, PSP and CBS can also manifest secondary CNS iron overload.

10.8 Primary familial brain calcification

Previously referred to as Fahr's disease or Fahr's syndrome, PFBC represents a clinically and genetically heterogeneous group of disorders characterized clinically by progressive parkinsonism, psychiatric features and cognitive decline, and radiologically by excessive calcium deposition in the basal ganglia (which requires CT rather than MRI scanning to confirm) (Batla et al., 2017). The genetic landscape of these disorders has been clarified in recent years, with the identification of dominantly inherited causative genes including *SLC20A2, PDGFB, PDGFRB* and *XPR-1*, which are either directly or indirectly involved with phosphate transport (Batla et al., 2017). Important differentials meriting consideration in all cases include pseudohypoparathyroidism or pseudopseudohypoparathyroidism, as well as mitochondrial disease. Certain clinico-radiologic features may suggest an underlying genetic abnormality, such as pronounced involvement of the dentate and thalamus (SLC20A2), headaches (PDGFB), cognitive dysfunction (XPR1) and seizures (pseudohypoparathyroidism) (Batla et al., 2017).

10.9 Manganism

Excess manganese deposition in the brain can result from a number of different disorders including occupational exposure (e.g. welders), ilicit drug use (abuse of the psychostimulant ephedrone, which uses potassium permanganate as an oxidizing agent), liver disease (acquired hepatolenticular degeneration) and genetic disorders in the manganese transporter (Butterworth, 2013; Kwakye, Paoliello, Mukhopadhyay, Bowman, & Aschner, 2015; Rose et al., 1999; Sikk, Haldre, Aquilonius, & Taba, 2011; de Bie, Gladstone, Strafella, Ko, & Lang, 2007; Tuschl et al., 2012; Tuschl et al., 2016). All of these disorders manifest with akinetic rigid parkinsonism. Pallidal T1 hyperintensity is the characteristic MRI signature of the disorder (Tuschl et al. 2008; Quadri et al., 2012).

10.10 Wilson's disease (copper deposition)

Brain MRI tends to be abnormal, showing T2 signal hyperintensity in the basal ganglia, pons and thalamus as well as a degree of brain atrophy. The characteristic 'face of the giant panda' seen on axial midbrain imaging, as well as its pontine counterpart, the' face of the panda cub', are mostly encountered in advanced disease (Mulroy et al., 2019).

10.11 Other

Though *focal brain lesions* should always be borne in mind, especially when dealing with significantly asymmetric presentations, secondary parkinsonism caused by focal structural pathology is rare. Parkinsonism may result from lesions outside the nigrostriatal tracts-including the cortex (especially frontal), basal ganglia, substantia nigra and brainstem (Bhatia & Marsden, 1994; Joutsa et al., 2018). Despite such lesions being anatomically remote, they appear to functionally connect to a common network, suggesting network-level disruption as the cause of parkinsonism (Joutsa et al., 2018).

Diffuse brain lesions including osmotic demyelination syndromes, various leucodystrophies and leucoencephalopathies, multiple sclerosis, mitochondrial disease and gliomatosis cerebri and have all been reported to cause parkinsonism (Brown, 2000; Jang et al., 2013; Molho, 2004; Saidha, Mok, Butler, Fanning, & Harrington, 2010; Slee, Pretorius, Ansorge, Stacey, & Butterworth, 2006; Sundal et al., 2013).

10.12 Pitfalls in interpretation of DAT SPECT

DAT SPECT imaging using ligands directed against the pre-synaptic dopamine transporter (DAT) identifies nigrostriatal degeneration with a high degree of accuracy. DAT imaging is abnormal in PD, and in most of the neurodegenerative atypical parkinsonian disorders, though in CBS DAT changes may be absent early in the disease course (Cilia et al., 2011) and DAT is normal in up to half of MSA-C cases (Jeong, Cheon, Kang, & Kim, 2017; Vergnet et al., 2019). Equally, abnormal DAT imaging does not restrict diagnoses to PD and non-genetic atypical parkinsonian disorders. Indeed, abnormal DAT imaging is seen in up to 70% of VP cases (often with symmetrical uptake reduction) (Antonini et al., 2012; Zijlmans et al., 2007), half of patients with NPH (Broggi et al., 2016), as well as being frequently abnormal in HD (Gamez et al., 2010), some SCAs and certain NBIAs.

11. Conclusion

The syndrome of parkinsonism, defined primarily by its motor manifestations of bradykinesia and tremor or rigidity, is now best conceptualized as network dysfunction disorder. Affectation of many areas within this circuit, or their connections, can lead to parkinsonism, hence the array of disorders causing this clinical syndrome is vast. The presence of parkinsonism opens a panoply of differential diagnoses. While ancillary testing e.g. structural neuroimaging, DAT SPECT imaging, can help in narrowing this, clinical examination searching for poignant signs remains the backbone of accurate diagnosis, and thence treatment. A structured, systematic approach to parkinsonism is paramount in clinical practice, in order to arrive at the correct diagnosis and offer the best treatment to patients.

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