Secondary Parkinsonism

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UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

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Secondary Parkinsonism

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Abbreviations

PD: Parkinson's Disease

DLB: Dementia with Lewy bodies

MSA: Multiple system atrophy

PSP: Progressive supranuclear palsy

CBD: Corticobasal degeneration

NPH: Normal pressure hydrocephalus

TRH: Thyrotropin-releasing-hormone

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1. Abstract

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Parkinson's Disease is the second most prevalent neurodegenerative disorder after Alzheimer's. In the context of an aging population, the incidence rates are set to rise even more. At the same time, Parkinson's Disease is a highly heterogeneous disorder, a real challenge in diagnosis and treatment. First mentioned in 1817, it is defined by the classical triad of resting tremor, bradykinesia, and rigidity. Besides the primary, idiopathic Parkinson's Disease, different atypical parkinsonian syndromes and numerous secondary causes have been identified. In this review, we focused primarily on the secondary etiologies of parkinsonism, which are both a challenge and a chance for efficient treatment of Parkinson's Disease. The most prevalent secondary etiologies include vascular, drug-induced parkinsonism, tumors, neuroinflammation, and metabolic dysregulation. We discussed the features that help identify and differentiate each entity and showed points for further research. In the context of current exclusively symptomatic treatment of parkinsonism with dopaminergic therapy, identifying underlying, treatable causes is extremely important. Neuroimaging is the diagnostic modality of choice since most etiologies of secondary parkinsonism show specific changes on magnetic resonance imaging scans. Furthermore, investigating the pathophysiologic processes of the etiologies of secondary parkinsonism could help understand the disease progression and show possible treatment strategies in future research.

2. Sažetak

Sekundarni Parkinsonizam

Kilian Wieland

Parkinsonova bolest je drugi najrašireniji neurodegenerativni poremećaj nakon Alzheimerove bolesti. U kontekstu sve većeg starenja stanovništva, incidencija bolesti još više raste. U isto vrijeme, Parkinsonova bolest je visoko heterogeni poremećaj, a samim time i veliki izazov u dijagnozi i liječenju. Prvi puta opisana 1817. Godine, definirana je klasičnom trijadom tremora, bradikinezije i ukočenosti. Osim primarne, idiopatske Parkinsonove bolesti, identificirani su različiti atipični parkinsonijski sindromi i brojni sekundarni uzroci. U ovom smo se pregledu usredotočili prvenstveno na sekundarne etiologije parkinsonizma, koje su i izazov i prilika za učinkovito ralikovanje, a samim time I liječenje Parkinsonove bolesti. Najčešći sekundarne uzroci uključuju vaskularni, lijekovima-inducirani parkinsonizam, tumore, upalne bolesti središnjeg živčanog sustava i metaboličku disregulaciju. Razmatrane su značajke koje pomažu u prepoznavanju i razlikovanju svakog entiteta i prikazani su ciljevi za daljnja istraživanja. U kontekstu trenutnog, isključivo simptomatskog liječenja parkinsonizma dopaminergičkom terapijom, identificiranje primarnih, a time I lječivih uzroka je izuzetno važno. Slikovne pretrage mozga su dijagnostička metoda izbora, jer većina uzroka sekundarnog parkinsonizma pokazuje specifične promjene na skeniranju magnetskom rezonancijom. Nadalje, istraživanje patofizioloških procesa etiologije sekundarnog parkinsonizma moglo bi pomoći u razumijevanju napredovanja bolesti i pokazivanju mogućih strategija liječenja u budućim istraživanjima.

3. Introduction and History of Parkinsonism

Parkinson's disease (PD) is among the neurological disorders with the most significant rise in incidence over the last years. From 1990 until 2015, the number of people with PD doubled to more than 6 million, which is expected to double again by 2040 (1). Especially in the context of the growing age of our population, we can expect this effect to accelerate even more.

Going back in time, the symptomatology typical of PD was first described by James Parkinson (1755 - 1824). In his essay "An Essay on the Shaking Palsy," published in 1817, he analyzed three of his own patients and three people he saw on the street. Already back then, he could describe the key features we associate today with PD , such as resting tremors, festination, and flexed posture, naming this disease the "Shaking Palsy." Even though he did not note the nowadays with PD associated features of bradykinesia and rigidity, James Parkinson assumed the underlying etiology must be found somewhere in the flow of innervation to the affected body part.

Only around 60 years later, in 1877, this disease was named after James Parkinson by Jean-Martin Charcot, who also recognized the until then missing features of bradykinesia and rigidity and determined that the patients are not essentially suffering from weakness, as suggested by the term palsy. It is astonishing how detailed Parkinson already described tremors over 200 years ago, differentiating between resting and movement tremors and correctly associating the resting tremor with PD, with its typical unilateral onset usually starting with the upper extremities before also affecting the lower limbs (2).

Two hundred years later, after James Parkinson described some of the features of PD for the first time, we are still faced with challenges around the etiology and management of this disease. Due to its broad clinical presentation and its numerous different secondary causes, there is room for research and investigation in the years to come.

4. Epidemiology of Parkinson's Disease

Incidence rates of PD range from around 8 to 18 cases per 100,000 in the general population, making it the second most prevalent neurodegenerative disorder after Alzheimer's disease (3). The main risk factor for PD is the age of the patient. Studies have shown an increase in the prevalence of 5 to 10 times from the age of 60 to the age of 90. In the context of the aging of the global population, we can expect a rise in the prevalence of PD in the years to come. Besides the age, male sex is another prominent risk factor, increasing the lifetime risk for PD nearly twofold compared to female patients. General risk factors seem to be genetic and environmental, making a multifactorial the most probable etiology. Research of familial cases of PD identified specific genes associated with the disease. However, their penetration and occurrence were only confirmed in around 5-10 % of cases, making environmental and behavioral factors the most relevant influencers. Specifically, gene mutations affecting the autophagy-lysosomal clearance pathway and synthesis of alpha-synuclein aggregates, such as SNCA, LRRK2, and GBA mutations, are linked to an increased risk for PD (4). Alpha-synuclein aggregates are nowadays thought to play a central role in the pathology of PD, even though the exact mechanism remains unclear (5). Environmental risk factors include exposure to certain toxins, lifestyle, repeated head injuries, and trauma. More research is needed to identify further environmental risk factors, which could help in the future treatment and prevention of PD.

5. Signs and Symptomatology of Parkinson's Disease

PD is classically defined by the triad of bradykinesia, rigidity, and tremor. Bradykinesia is seen in the patients as problems with the initiation and speed of repetitive movements. Typically, when patients are asked to walk a certain distance, one can see a delayed onset of walking, slow steps, and a delayed movement stop. Further features of the bradykinesia are hypomimia and micrographia, the reduced handwriting size. According to the UK Parkinson's Disease Society Brain Bank, the clinical diagnostic criteria of bradykinesia is the essential feature for diagnosing PD. Additionally, the patient must present at least one of the following symptoms: muscular rigidity, resting tremor, or postural instability (6). These primary motor

symptoms can be accompanied by numerous non-motor symptoms, which can be categorized into disturbances of autonomic function, sleep disturbances, psychiatric and cognitive disturbances, and sensory symptoms. Autonomic disturbances include gastrointestinal symptoms, orthostatic hypotension, problems with urinary control as well as dermatologic problems, such as excessive sweating. The neuropathologic changes in PD also affect the physiologic sleeping cycle, causing fractioned and more shallow sleep, a tendency of frequent awaking, and a higher prevalence of sleep syndromes. Due to the lack of sufficient sleep during the night, increased daytime sleepiness can be observed. Neuropsychiatric symptoms range from visual hallucinations and illusions over cognitive deterioration and dementia to depression and anxiety. While initially, the hallucinations are primarily visual and non-threatening to the patients, with the progression of the disease, patients develop more psychotic hallucinations with persecutory ideas. Of increasing relevance are dopaminergic dysregulation syndromes, such as high risk-taking behavior, gambling, or driving at high speeds. This is more common in patients with the onset of the disease at a relatively young age. Problems with executive functions, such as planning and organizing, visuospatial dysfunction, and memory impairment are among the most frequent symptoms grouped under cognitive disturbances of PD. Depression and anxiety account for another joint group of symptoms associated with PD. They are primarily related to the severity of the disease and may improve under treatment. However, during the long clinical course of the illness, they may reoccur. Long before the motor symptoms of PD, patients might begin to experience sensory symptoms. The most common and earliest sensory symptom is reduced or lost sense of smell, occurring in over 80 % of patients (7). Pain is another relevant sensory symptom of PD, especially after several years with the disease. Different types of pain in PD have been identified, such as musculoskeletal, dystonia-related, or neuropathic pain, among others (8). PD has a slow onset and late deterioration, with the course of the disease going well over ten years. Compared to the general population, the relative mortality risk is 1.6-3.0 (9). Increased age and dementia are the most relevant factors for increased mortality.

6. Primary vs. Secondary Parkinsonism

As mentioned before, the first diagnostic step according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria is the presence of bradykinesia, together with at least one other typical sign of Parkinsonism, such as resting tremor, muscular rigidity, or postural instability. Once this diagnostic criterion is fulfilled, the patient is diagnosed with an entity of the Parkinson's syndromes. As the next step, we need to differentiate between primary and secondary PD and exclude the syndromes of atypical Parkinsonism. Grouped under atypical Parkinsonism is dementia with Lewy bodies (DLB), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD). They all have increased deposition of alpha-synuclein and tau in common, showing specific symptoms depending on the exact location of the deposits. Only later on do they develop typical features of Parkinsonism (10). In the second step of the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria, all possible symptoms are identified that might indicate parkinsonian syndromes with their specific neuropathologic changes. Vascular, drug-induced, tumor-related, or metabolic parkinsonism are just a few entities grouped under parkinsonian syndromes or secondary parkinsonism. Only once all these possible etiologies are excluded can the patient be diagnosed with primary, idiopathic PD. In this review, we will discuss the secondary etiologies of parkinsonism in more detail.

6.1. Vascular Parkinsonism

Vascular Parkinsonism is a controversially discussed entity within the Parkinsonian syndromes. Due to its broad heterogenicity and symptomatic spectrum, it remains challenging to clearly define both pathologic background and associated symptomatology. The concept of vascular parkinsonism was for the first time brought up by Macdonald Critchley in 1929, who described the connection between cerebrovascular disease and parkinsonian features as a subvariety of PD with distinctive symptoms (11). In 1987, subcortical atherosclerotic encephalopathy (SAE) was associated with a gait disorder called lower-body parkinsonism (12). The greatest challenge remained to find a clear, precise definition of vascular parkinsonism that gave the possibility to distinguish the specific features and etiology

of vascular parkinsonism from other secondary causes as well as idiopathic PD. Only in 2004, a research article proposed the following diagnostic criteria for vascular parkinsonism: 1. The presence of parkinsonism; 2. Confirmed evidence of cerebrovascular disease; 3. There must be a correlation between cerebrovascular disease and parkinsonism symptoms (13). Depending on the onset and predominant features, Rektor et al. suggested three different subtypes of vascular parkinsonism: 1. The acute to subacute type of onset after a single vascular event and lesion at a location consistent with symptoms of parkinsonism; 2. A more insidious form of onset that occurs in the context of white matter lesions (WML); 3. A mixed type that has white matter lesions and a neurogenerative component (14). White matter lesions, as a marker of small vessel disease of the brain, are an essential indicator of chronic and progressive vascular disease. Interestingly, some papers question the previously mentioned definitions. In these publications, only the first subtype, involving lesions in the substantia nigra and the nigra-striatal pathway caused by either hemorrhagic or ischemic stroke, is considered "true" vascular parkinsonism (15). Vascular parkinsonism presents primarily with motor symptoms of the lower body. Distinctive symptom constellations can be seen in specific subtypes of vascular parkinsonism and, therefore, could be diagnostic, even though they are neither specific nor always present individually. The first subtype of vascular parkinsonism, caused by focal lesions after a preceding stroke, presents clinically with non-progressive hemiparkinsonian signs, depending on the exact location of the focal lesion within the substantia nigra or the nigrostriatal pathway. While of lesser prevalence, bilateral symptoms are also possible. The insidious onset subtype is a progressive form of vascular parkinsonism with a rather heterogeneous picture of symptoms but predominance for the lower body. Gait disorder, rigidity, corticospinal disturbances, and urinary problems are possible symptoms. Problematic, especially for the elderly, is the early postural instability with its associated increased risk for falls. Patients with the mixed subtype of vascular parkinsonism meet the diagnostic criteria of PD or atypical parkinsonism but also show on imaging diagnostics signs of cerebral vascular disease (14). Magnetic resonance imaging (MRI) is the gold standard for diagnosing vascular parkinsonism since it shows recent cerebrovascular events and WML, both diagnostic prerequisites for vascular parkinsonism (16). Regarding the treatment, the reduction of cardiovascular risk factors plays a vital role in preventing the development of vascular parkinsonism. Dopaminergic replacement

therapy has shown to be effective in around 30 % of patients with vascular parkinsonism (17) and should therefore be considered for pharmaceutical treatment. Furthermore, patients with the insidious subtype of vascular parkinsonism might profit from therapeutic lumbar puncture, as it is not always possible to distinguish it clinically from the parkinsonism caused by normal pressure hydrocephalus (NPH). Even though further research is needed, the therapeutic lumbar puncture could be considered in patients with lower body parkinsonism (18).

6.2. Drug-Induced Parkinsonism

Drug-Induced Parkinsonism is another prevalent entity among the secondary parkinsonism syndromes. Despite significant variability in the exact incidence of Drug-Induced Parkinsonism depending on the study type, it is one of the most prevalent secondary parkinsonism syndromes. In a large-scale study from Japan, drug-induced parkinsonism has been identified as the second leading etiology of parkinsonism after idiopathic PD (19). Drug-induced parkinsonism was defined as the occurrence of parkinsonism-typical symptoms after treatment with dopamine-impairing drugs in patients without a previous PD history. Additionally, the symptoms are expected to improve within six months after discontinuing the offending drug (20). However, many studies criticized this definition as too restrictive, excluding cases that might actually be drug-induced parkinsonism but are not accounted for because they did not take a drug directly influencing the nigrostriatal pathways or they only improved after more than six months after discontinuation of the drug (21). Drugs suspected to cause drug-induced parkinsonism can be grouped according to their risk. Counted to the high-risk group are the classical central dopaminergic antagonists such as first-generation antipsychotics and calcium channel blockers such as flunarizine and cinnarizine. Other offending drugs are H1 antihistamines and antidepressants such as SSRIs (22). This shows that the limitation to drugs that affect the nigra-striatal pathways as diagnostic criteria might be too narrow. Furthermore, as both mentioned studies showed, certain drug classes tend to cause drug-induced parkinsonism with a delay of over one year. Especially the calcium channel blocking agents such as flunarizine showed this tendency (22). Considering these findings, the precise definition and diagnostic criteria of drug-induced

parkinsonism remain challenging. Clinically, drug-induced parkinsonism is quite heterogeneous, showing different symptomatic constellations depending on the offending drug type. Generally, drug-induced parkinsonism is clinically described as a bilateral symmetric syndrome of acute to subacute onset, infrequently showing the typical parkinsonian tremor (23). Furthermore, drug-induced parkinsonism does not respond as well to Levodopa as PD (24). Besides these features, it might be challenging to differentiate drug-induced parkinsonism from idiopathic PD. In recent years, several studies aimed to evaluate the differences in non-motor symptoms and the use of imaging modalities as additional support to make the correct diagnosis. Hyposmia has been identified as a non-motor symptom typical for idiopathic PD but primarily absent in drug-induced parkinsonism patients. Therefore, the Sniffin' Sticks test (SST) might be an additional diagnostic tool to differentiate drug-induced parkinsonism from idiopathic PD (25). However, other secondary causes of hyposmia, such as smoking, limit the diagnostic sensitivity. Another promising diagnostic tool is the cardiac MIBG scintigraphy, measuring the MIBG uptake in the heart. Lee et al. identified a cardiac MIBG uptake within the normal range in most patients with suspected drug-induced parkinsonism, which is usually reduced in idiopathic PD (26). All mentioned studies indicated another problem. In a subset of patients with drug-induced parkinsonism, the symptoms did not improve after discontinuing the offending drugs but either remained stable or even deteriorated into several PD. This indicates that drugs suspected to cause drug-induced parkinsonism might unmask an early state of idiopathic PD, accelerating the progression. In a relatively recent study, Jeong et al. suggest drug-induced parkinsonism as a predictor of later development of idiopathic PD (27). Drug-induced Parkinsonism, with its high prevalence and possible trigger point for idiopathic PD, should therefore be kept in mind by every physician prescribing relevant drugs, especially in the elderly.

6.3.   Normal Pressure Hydrocephalus

Normal-pressure hydrocephalus (NPH) is defined by the classical Hakim's triad of gait disturbance, urinary incontinence, and cognitive impairment. Several studies focused on the occurrence of parkinsonian features in the setting of NPH and what

would be the best diagnostic and therapeutic approach. A population-based study from 2017 found in most patients with radiologically and clinically confirmed NPH a higher occurrence of symptoms typical for parkinsonism, such as bradykinesia, rigidity, and postural instability (28). The resting tremor was not recognized more frequently than within the control group, and the in idiopathic PD typical asymmetric onset of symptoms was not observed. Söderström et al. recommend the early consideration of secondary causes of parkinsonian symptoms in patients with parkinsonism refractory to dopaminergic therapy. Diagnostically, neuroradiological imaging is the best modality for NPH and should be liberally used if this etiology is suspected. Nevertheless, the precise diagnosis and connection between NPH and parkinsonism remain challenging. Therapeutically, studies have shown that patients benefit the most from ventriculoperitoneal shunts and oral dopaminergic therapy (29).

6.4. Tumor related Parkinsonism

One of the rarer etiologies of parkinsonian symptoms is brain tumors. Brain tumors infiltrating and compressing the midbrain most frequently can be associated with a higher chance of presenting with parkinsonian symptoms (20). Typically, parkinsonism related to brain tumors presents as akinetic-rigid syndrome with a unilateral manifestation and neurologic deficits involving movement of the eyeballs and pyramidal or cerebellar signs. Additionally, like most secondary parkinsonian syndromes, parkinsonism due to brain tumors tends to have poor responsiveness to dopaminergic treatment (30). Especially in patients with additional symptoms besides the typical parkinsonian features, one should be suspicious of an ongoing mass lesion that could explain these symptoms, depending on the location. Furthermore, brain tumors can cause secondary obstructive hydrocephalus, which is, as previously discussed, also associated with the development of parkinsonism. Again, similarly to other secondary causes of parkinsonism, early diagnosis and treatment are essential for a favorable outcome. The key diagnostic tool is neuroradiologic imaging. Case studies have shown that, if detected early on, parkinsonism due to brain tumors tends to improve substantially or even be reversible after the removal of the tumor and release of the compression (31).

6.5. Toxic etiologies of secondary parkinsonism

Besides the previously discussed structural and more common etiologies of secondary parkinsonism, there are also rare cases of parkinsonism after exposure to certain toxic substances. For some toxins, there are only a few reported cases in the literature, while others are generally suspected to be causative of parkinsonian symptoms. In several studies, manganese exposure has been associated with a higher risk of secondary parkinsonism (32). As a basal ganglia toxin, it causes degeneration of the globus pallidum by disrupting normal mitochondrial function. Furthermore, inhibiting glutamate transport increases intracellular glutamate, leading to cytotoxicity. Symptomatically, manganese-induced parkinsonism shows early postural instability, bradykinesia, rigidity, a high-stepping gait sometimes referred to as "cock-walk", and a low response rate to L-dopa therapy. T1 hyperintensity in the striatum and globus pallidum on MRI and regular DaT SCAN should raise the suspicion of manganese-induced parkinsonism. Therapeutically, chelation therapy with Calcium EDTA showed promising results (33). Of the heavy metals, mercury is the most toxic in many ways but is also associated with a high risk of secondary parkinsonism. This can be explained by the high sensitivity of nigral dopaminergic neurons to mercury. The toxic effect is even more pronounced by synergistic effects after exposure to other metals such as iron, copper, or lead. Cases of parkinsonism have also been reported after intoxication with carbon monoxide, with incidence rates of around 9.5 % of those with CO poisoning (34). While the exact mechanism is still not completely understood, bilateral damage to the globus pallidus is the most probable underlying pathology. Diagnosis is difficult since specific changes on MRI, such as lesions in the globus pallidus, can be found in all patients with CO poisoning, regardless of whether they develop secondary parkinsonism. Symptoms are similar to other parkinsonian syndromes, namely gait disturbances, impaired mentality, and urinary incontinence. Resting tremor is not commonly seen. There is no broadly accepted specific therapy or prevention since, similar to other secondary parkinsonian syndromes, the response rate to dopaminergic treatment is limited. Promising results have been shown with anticholinergic therapy. Besides the mentioned toxins, some other substances are also associated with parkinsonism. The most frequently mentioned ones are cyanide, methanol, organophosphates,

hydrocarbons, and organochlorides. For patients showing parkinsonism with a history of exposure to one of these toxins, one should always consider a correlation between the exposure and the symptoms, which is especially important regarding the management and therapy.

6.6. Metabolic parkinsonism

Metabolic syndrome is associated with a 1.5-fold increase in all-cause mortality and increases the risk for cardiovascular events by 2-fold (35). Commonly it is defined as a complex of symptoms and conditions that all share a similar pathophysiological pathway and lead to increased disease burden and mortality. Depending on the study group, different criteria exist. Generally, obesity, hyperglycemia, and dyslipidemia are the most relevant features of metabolic syndrome (36). Several studies evaluated the connection between metabolic syndrome and parkinsonism. Nam et al. found 2018 in a large-scale nationwide cohort study in South Korea indicators that metabolic syndrome might be a risk factor for secondary parkinsonism (37). After correcting for confounding errors, every component of metabolic syndrome was associated with an increased risk for parkinsonism. Furthermore, the more individual components of metabolic syndrome a patient has, the higher the overall risk for secondary parkinsonism. In 2021, Park et al. showed that prevention and improvement of metabolic syndrome also substantially decreased the parkinsonism risk (38). These studies clearly show that metabolic syndrome and metabolic derangements increase the risk for parkinsonism, besides being risk factors for several other diseases, primarily cardiovascular diseases. Essential therapy is the prevention by modification of the individual components of the metabolic syndrome.

6.7. Thyroid Diseases

The dopaminergic system and hypothalamic-pituitary-thyroid axis are an interconnected network. Therefore, the assumption could be made that disturbances in one system also influence the other system. Despite that, only recently have studies focused on the increased risk for secondary parkinsonism in patients with

thyroid disease. After several studies postulated that thyroid abnormalities and parkinsonism might share common pathophysiologic mechanisms, Kim et al. in 2021 used the Korean National Health Screening Cohort to show possible connections (39). They found that both hyperthyroidism and hypothyroidism increased the risk of secondary parkinsonism. For men, the increased risk is mainly in those older than 70, while in women, it is primarily in those under 70. This study proves the previously stipulated association and provides the basis for further investigations related to the shared pathophysiology and possible common therapeutic approaches. However, different studies already went one step further and showed potential shared treatment options for thyroid diseases and parkinsonism. For example, due to the interconnected pathways, TRH analogs and levothyroxine might be potential candidates for treating parkinsonism. This is due to their stimulatory influence on the dopaminergic system and their neuroprotective effects (40). In addition, there is already limited evidence of shared genetic risk factors, which might become relevant for screening in the future. In conclusion, it is essential to recognize the shared pathophysiology of parkinsonism and thyroid diseases and their influence on one another.

6.8. Type 2 Diabetes Mellitus

As discussed, hyperglycemia as one metabolic syndrome entity increases the overall lifetime risk for parkinsonism. Besides hyperglycemia, several studies have investigated insulin resistance as another risk factor for secondary parkinsonism. Dysregulation of the insulin signaling pathway might cause neurodegeneration, amyloid aggregation, neuroinflammation, and mitochondrial dysfunction (41). All these contribute to the development and faster progression of secondary parkinsonism. In addition, different hypoglycemic drugs have been studied for their effect on secondary parkinsonism. GLP1 agonists have shown promising results in rodent models; however, these models do not correlate well with the complex human disease. Newer formulations, such as dual GLP1/GIP receptor agonists with a longer half-life, showed positive results in clinical trials, even though long-term safety and efficacy are still to be determined. DPP4 inhibitors also showed a lower incidence of

parkinsonism than the control group, which provides the basis for further research regarding the use of those hypoglycemic drugs against parkinsonism (42).

6.9. Wilson's Disease

Wilson's Disease is a hereditary, autosomal recessive disorder of the copper metabolism in the liver. Caused by a mutation of the ATP7B gene on chromosome 13, Wilson's Disease leads to the accumulation of copper in the liver, resulting in the typical hepatic and neurological symptoms (43). The latter include movement disorders as the most prominent sign, ranging from tremor, choreiform movements, akinetic rigid syndrome, and rigid dystonia to full-blown parkinsonism. Due to the congenital genetic etiology of Wilson's Disease, these neurological signs typically appear around the age of 20. Therefore, younger patients presenting with parkinsonian symptoms and potentially additionally some liver dysfunction should raise the suspicion of Wilson's Disease. Since early recognition and initiation of therapy is of the highest importance for a favorable outcome, the diagnostic workup should be started immediately. Compared to other etiologies of secondary parkinsonism, tremor seems much more frequent, making it difficult to differentiate from idiopathic Parkinson's disease at times. Furthermore, additional challenges arise from the significant variance of neurologic symptoms different patients with Wilson's Disease might present (44). Besides genetic testing for mutations of the ATP7B gene and the usual clinical checkups and history taking, cerebral MRI, serum copper caeruloplasmin, 24-hour urinary copper excretion, and ophthalmologic examination are part of the diagnostic workup of Wilson Disease. Cerebral MRI typically shows lesions in the putamen, globus pallidus, caudate, thalamus, and pons, all relevant cerebral locations associated with parkinsonian symptoms. If recognized early, treatment is promising with penicillamine or trientine as first-line treatment. Due to the genetic mutation, life-long therapy is necessary with strict adherence to the therapeutic scheme.

6.10. Inflammatory secondary parkinsonism

As discussed in the beginning, alpha-synuclein aggregation plays a central role in the etiology and progression of parkinsonism. Studies have shown that chronic inflammation in the brain and the enteric system favors the accumulation of alpha-synuclein (45). This is additionally supported by reported cases of parkinsonism after infections with viral pathogens such as influenza A, Herpes-simplex virus-1, or varicella-zoster virus in the context of an encephalitis lethargica (46). Pathogens are assumed to enter the central nervous system through the nasal mucosa and olfactory pathway and through the gastrointestinal mucosa, the enteric plexus, and preganglionic fibers of the vagal nerve. They cause neurodegenerative and neuroinflammatory changes in the nigrostriatal pathway (45). Furthermore, viral particles of Herpes simplex virus-1 and Eppstein-Bar-Virus directly promote alpha-synuclein aggregation along with the accumulation of intracellular deposits such as Lewy Bodies. All of these promote the progression of parkinsonism and might be trigger points for causing secondary parkinsonism. Even though there are limited studies, first case reports show parkinsonian-like symptoms after infections with SARS-CoV-2 (47). The shared inflammatory etiology of several parkinsonian syndromes could also be used as a potential therapeutic target for immunomodulatory treatments. This has to be further investigated in future research since studies have not shown consistent results (45).

7. Treatment of Parkinsonism

Parkinsonism with all different entities ranging from idiopathic PD over parkinsonian syndromes to secondary parkinsonism is a highly heterogeneous disease where every patient shows individual features and symptom constellations. Therefore, the primary therapy is still symptomatic instead of actually targeting the underlying pathologic mechanisms, slowing the progression, or even preventing parkinsonism from appearing at all. According to current guidelines, there is no single first-line treatment option, but levodopa-preparations, dopamine agonists, and Monoamine oxidase-B inhibitors are all possible initial treatment modalities. Which of those is the best option depends on the individual features of the patient, especially the comorbidities, age, and symptom constellation. To prevent peripheral dopaminergic side effects such as hypotonia and to increase dopamine availability in the central

nervous system, it is recommended to combine levodopa-preparations with a decarboxylase-inhibitor such as carbidopa or benserazide. With further progression or appearing of first signs of wearing-off of the initial treatment, increasing dosages and add-on therapy with another drug class are options. Enteral infusion via jejunal pump or unilateral and bilateral deep brain stimulation are available in advanced disease. Besides these symptomatic drug therapies, physiotherapy, regular exercise, and cognitive therapy might help slow disease progression (48). However, these drug therapies only focus on symptomatic treatment instead of targeting the underlying pathophysiologic processes. Therefore, it is essential to exclude in a first step all secondary parkinsonism etiologies and initiate specific, focused treatment for those. Furthermore, current research focuses on targeting the specific underlying disease processes, such as alpha-synuclein aggregation, microglial activation, or neuroinflammation. Challenges arise from the mentioned heterogenicity of patients with parkinsonism and the study designs. With further research and new and advanced study designs, there might be a chance to target specific pathophysiological pathways before the actual parkinsonian symptoms arise (49).

8. Conclusion

As one can see, secondary parkinsonian syndromes have extremely widespread, diverse etiologies, making them a real challenge in daily practice. Furthermore, the symptomatology of patients suffering from parkinsonism is quite heterogeneous, making it even more difficult to find universal diagnostic and therapeutic guidelines and algorithms. On the other hand, treatment modalities of parkinsonism are, to date, focused primarily on symptomatic therapy instead of acting on the underlying pathophysiologic mechanisms, which would prevent the disease or at least slow down the progression. Therefore, it is essential to keep the etiologies of secondary parkinsonian syndromes in mind since most of them can be treated with a favorable outcome of the motor and non-motor symptoms of parkinsonism. For the correct diagnosis, all secondary causes of parkinsonism and atypical parkinsonian syndromes must be excluded as a first step. Only once that is fulfilled should one give the diagnosis of primary, idiopathic PD. This shows the extensive diagnostic workup necessary for patients suffering from parkinsonian symptoms. Only through

this approach is it assured that no underlying etiology is missed, which could be treated instead of initiating symptomatic treatment with dopamine replacement. Especially neuroradiologic imaging has shown to be a valuable diagnostic tool, as it might reveal unique features of specific etiologies of secondary parkinsonism, such as in vascular parkinsonism, NPH, or tumor-related parkinsonism. Additionally, the medication plan could give valuable information on drug-induced parkinsonism. As discussed in the relevant chapter, besides the typical drug classes, such as antipsychotics, several other frequently prescribed drugs are associated with increased risk for parkinsonism. Furthermore, the early onset of parkinsonism should raise suspicion, and congenital etiologies such as Wilson's Disease must be excluded. As the last step, therapeutic resistant symptoms during levodopa treatment also point towards a secondary cause of parkinsonism. In conclusion, despite parkinsonism being a highly complex group of diseases, with a thorough workup and step-by-step exclusion of one underlying etiology after the other, it is possible to get to the proper diagnosis and help the patient more directly by treating the underlying problem instead of just the symptoms. Nevertheless, there is still room for further research, especially towards specific treatment modalities for the pathophysiologic processes leading to PD symptom complexes.

9. Acknowledgements

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11. Biography

Kilian Wieland was born in Munich, Germany, and grew up in the Bavarian countryside. During high school, he discovered his interest in the human body and medicine, which was further strengthened after a hiking accident in the Italian Alps. Being fascinated by the international environment during his work and travel time in the US, Kilian enrolled at the University of Zagreb, School of Medicine, to study medicine.

Besides playing tennis and the piano, Kilian enjoys spending his free time outside in the nature, during the summers hiking in the alps, while he can be found skiing during the winter.