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Precision Dopaminergic Treatment in a Cohort of Parkinson's disease Patients Carrying Autosomal Recessive Gene Variants: Clinical Cohort Data and a Mini Review

Christos Koros [1,*], Athina-Maria Simitsi [1], Nikolaos Papagiannakis [1], Anastasia Bougea [1], Roubina Antonelou [1], Ioanna Pachi [1], Evangelos Sfikas [1], Evangelia Stanitsa [1], Efthalia Angelopoulou [1], Vasilios C. Constantinides [1], Sokratis G. Papageorgiou [1], Constantin Potagas [1], Maria Stamelou [2] and Leonidas Stefanis [1]

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Abstract: Introduction: Parkinson's disease (PD) patients harboring recessive gene variants exhibit a distinct clinical phenotype with an early disease onset and relatively mild symptoms. Data concerning individualized therapy for autosomal recessive PD forms are still scarce. Methods: Demographic and treatment data of a cohort of PD carriers of recessive genes (9 homozygous or compound heterozygous PRKN carriers, 4 Heterozygous PRKN carriers and 3 biallelic PINK1 carriers) were evaluated. Results: The average Levodopa Equivalent daily dose (LEDD) was 806.8±453.5 (range 152-1810) in PRKN carriers and 765±96.6 (range 660-850) in PINK1 carriers. The majority responded to low/moderate doses of Levodopa. The response to Dopamine Agonists (DA) was often favorable both as initial and longitudinal therapy. 8/13 PRKN and 1/3 PINK1 carriers were treated with amantadine successfully, and this also applied to patients who could not tolerate Levodopa or DA. Conclusions: In the era of personalized treatment, the therapeutic approach in recessive PD gene carriers might differ as compared to idiopathic PD. Lower LEDD doses were efficient even in patients with a very long disease duration, while a few patients were doing well without any Levodopa treatment decades after disease initiation. DA or amantadine could be used as a first and main line treatment regimen if well tolerated. Literature data on therapeutic strategies in carriers of pathogenic mutations in recessive PD genes, including device-aided treatments will be further discussed.

Keywords: Parkinson's disease; genetic; recessive; treatment; Levodopa; dopamine agonists; amantadine

1. Introduction

The genetic background could likely explain a good part of the heterogeneity ob-served in progressive motor and cognitive decline among Parkinson's disease patients (PD). In monogenic forms of PD, specific mutations correspond to a defined pattern of clinical impairment. The stronger the association between genotype and alpha-synuclein pathology, the greater the risk is for severe motor and non-motor symptomatology. Interestingly, PD patients harboring recessive gene variants exhibit a distinct clinical pheno-type with an early disease onset (EOPD) and relatively mild symptoms.

Mutations in the gene encoding for Parkin (PRKN) are the most commonly identified genetic cause of EOPD [1,2]. The genetic deficit can be missense/nonsense mutations or a copy number variant (CNV) causing loss of function. Parkin is an E3 ligase, participating in the degradation of specific substrates through the ubiquitin-proteasome system. Its ex-act role in PD has yet to be

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clarified, but the evidence suggests involvement of Parkin at the level of mitochondria, in the process of proper removal of damaged mitochondria through mitophagy [3]. In terms of pathology PRKN related PD is a nigropathy and the most prominent finding is degeneration of neurons in the brainstem pigmented nuclei [4]. Notably, the loss of neurons was less prominent in the locus coeruleus than in the substantia nigra pars compacta. Lewy bodies are absent in the majority of cases and only in the post-mortem assessment of 3 patients, researchers have verified the presence of Lewy bodies with alpha-synuclein depositions. A few other affected individuals had neurofri-brillary tangles (Tau pathology) [5]. The phenotype of PRKN variants is characterized by a benign course with slow progression, a favorable response to levodopa or anticholinergic medications, common presentation as dystonia, especially in the lower extremities and frequent emergence of dyskinesias and motor fluctuations. Non-motor symptoms are less prominent than in idiopathic PD. Sleep benefit has been reported, and exercise-induced dystonia may be present, resulting in a rather demanding clinical differential diagnosis with Dopa-Responsive Dystonia (DRD) [1,6]. Psychiatric manifestations like anxiety, depression, obsessive-compulsive disorder-like symptoms and even frank psychosis might occur, sometimes antedating motor symptoms. Cognition is not affected even after very long disease duration and patients often perform better as compared to idiopathic PD [7,8]. Notably, imaging with DATSCAN SPECT in PRKN carriers reveals impaired dopaminergic innervation to the caudate nucleus even to a greater extent than in idiopathic PD [1].

Whether heterozygote Parkin mutations result in a PD phenotype is still elusive [9]. The importance of heterozygous mutations is rather controversial and could be explained by a gain of function or a negative effect, haploinsufficiency, and concomitant not easily identified mutations either within the Parkin gene (in trans), or within other genes. Addi-tional genetic, epigenetic or environmental factors might play a role in the clinical im-portance of heterozygous PRKN mutations. A recent study assessed how monoallelic or biallelic pathogenic variants in the PRKN gene may affect its transcription in peripheral blood mononuclear cells (PBMCs). A significant decrease in PRKN mRNA expression lev-els were observed in both heterozygous and biallelic PRKN PD carriers as compared to idiopathic PD and healthy controls [10]. Another study has shown a significant risk for PD only for heterozygote dosage variants and not for point mutation heterozygote carriers [11]. It is possible that in certain early onset PD patients, heterozygous dosage PRKN mu-tations might play a causal role while in late onset PD such mutations could be an inci-dental finding [2].

After Parkin, mitochondrial PTEN (phosphatase and tensin homologue)-induced ki-nase1 (PINK1) mutations appear to represent the second most common cause of EOPD. Missense, nonsense, splice mutations, or small deletions or insertions are encountered, either in a compound heterozygote or homozygous state. PINK1 is a kinase localized to the mitochondria and the mechanism of the disorder is considered to be a loss-of-function mitochondrial disease. Its exact role remains uncertain, but it appears to be involved in the pathway of mitophagy, acting upstream of Parkin. Furthermore, it may also have a role in the proper function of mitochondrial complex I [12]. Regarding pathology in PINK1 related PD literature data are scarce [4]. Autopsy in a compound heterozygote showed neu-ronal loss in the substantia nigra pars compacta while locus coeruleus was spared. Lewy body pathology was present and degeneration was also evident in the nucleus basalis of Meynert [13]. Phenotype involves a relatively early age of onset, a rather benign course, more frequent gait deficits and disease onset with lower limb problems, excellent response to levodopa therapy, and increased risk for dyskinesias. Notably, dementia is not typical of PINK1 patients even after long disease duration although cognitive deficits may occur in some patients [2,7]. As far as other non-motor symptoms are concerned, patients with PINK1 mutations often have decreased olfaction [14] while some may also manifest autonomic dysfunction [15]. Despite few previous studies, REM Sleep behavior disorder is rarely described, even in advanced cases [8,16]. Anxiety, depression, panic attacks or psychosis have been reported in certain cases and may even antedate motor symptoms [12,17].

An additional rare autosomal recessive form of EOPD is due to mutations in the Pro-tein deglycase DJ-1 gene, encoding for a protein which has a role in the antioxidant re-sponse, and may participate in common biochemical pathways with PINK1 and Parkin [3]. DJ-1 phenotype resembles that usually seen in Parkin-related PD including an early age of onset, slow progression, frequent occurrence of focal dystonia, good response to dopaminergic treatment but often prominent motor

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complications upon treatment, varia-ble cognitive involvement and psychiatric symptoms, especially anxiety [2,7].

The aim of the present study was to assess the dopaminergic therapy requirements of a cohort of PD patients carrying pathogenic mutations in recessive genes (Parkin, PINK1) and its outcome in terms of motor and non-motor competence of patients. Moreover, current literature data on conventional and device-aided treatments in this particular PD patient population will be reviewed.

2. Literature Data on Autosomal Recessive PD Device-Aided Therapies

Previous studies based on data derived from case series, have shown an overall fa-vorable response to Levodopa treatment, however literature evidence concerning individ-ualized therapy for autosomal recessive PD forms are still sparse. The majority of past re-search on PD carriers of recessive genes has focused mostly on device-aided therapies in advanced stages of the disorder [18–20]. Genetic PD variants with a full-blown phenotype which includes motor complications, psychiatric problems, cognitive deficits, impulse control disorders and peripheral neuropathy may require different therapeutic strategies. PRKN mutation carriers generally are considered to have a favorable response to Deep Brain Stimulation (DBS) treatment. In most studies, motor amelioration in the PRKN car-rier group was similar when single heterozygous PRKN mutations were excluded. A moderate or even poor response to DBS could be attributed to a non favorable initial re-sponse to L-Dopa prior to surgery in certain patients, to a more pronounced axial symp-tomatology and occasionally to improper target selection [20]. A study by Moro and co-authors [21] showed that following bilateral Subthalamic Nucleus (STN) DBS surgery, in 11 PRKN mutation carriers (6 biallelic and 5 monoallelic), approximately both muta-tion carriers and non carriers exhibited approximately 42% improvement in motor scales (UPDRSIII) 3-6 years post treatment. However, it was clear that response to DBS was not superior in PRKN carriers compared to non carriers and could be limited by more ad-vanced axial motor symptomatology at a rather early disease stage [21]. In another cohort, in 9 PRKN mutation carriers (4 biallelic and 5 monoallelic) patients underwent surgery with either bilateral STN DBS or bilateral GPi DBS. STN DBS resulted in greater decrease in motor scores, while GPI DBS patients exhibited a significant improvement in dyskinesias [22]. Lohmann and co-authors (2008) assessed a cohort which included 14 PRKN mutation carriers which underwent bitaleral STN DBS. Motor and non motor scores were comparable between carriers and sporadic PD, however Levodopa Equivalent dose (LEDD) was lower in PRKN carriers post surgery [23]. Similarly, Kim and co-authors did not report differences in motor and non motor scores between PRKN carriers and non-carriers but noted a 70% reduction in LEDD [24]. It appears that axonal symptoms like postural stability were worse in PRKN carriers than in non-carriers following STN DBS [24]. DBS is probably a safe option in terms of cognitive deterioration in PD patients carrying PRKN mutations. Moreover, there are no sufficient data regarding the impact of the type of PRKN mutations on the clinical outcome following DBS [19]. Continuous apomorphine subcutaneous infusion in PRKN was published as a case report and a marked improvement in dyskinesias and OFF time was reported. Moreover, the overall mobility was better and the falls became scarce. Oral dopaminergic medication could be decreased [25]. Finally, to our knowledge, there are very limited data on levodopa/carbidopa intesti-nal gel infusion (LCIG) in PRKN mutation carriers, with only one 1 case reported [26].

Studies on device aided therapies in PINK1 carriers are scarce and have only includ-ed case reports due to the rarity of carriers. Moro and co-authors [21] reported 40% im-provement in UPDRSIII score following STN DBS which was sustained in follow up. An-other case report showed a significant improvement in fluctuations and other motor symptoms. Impulse control disorder was ameliorated post treatment and non motor symptoms were relatively stable with the exception of hypersomnolence [26]. Finally, Bo-rellini and co-authors reported that after Bilateral GPi DBS in a PINK1 carrier, motor com-plications were improved but there was an increase in freezing 4 years post surgery [27,28]. No data on the outcome of LCIG or continuous apomorphine infusion regarding pathogenic PINK1 mutation carriers are available in the literature.

3. Materials and Methods

We assessed a cohort of PD carriers of pathogenic mutations in recessive genes : 9 were homozygous or compound heterozygous PRKN carriers (pathogenic mutations), 4 Heterozygous PRKN carriers and 3 biallelic PINK1 carriers, while no carrier of DJ-1 path-ogenic mutations could

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be identified. PRKN mutations included both point and dosage mutations. Co-existence of mild and/or severe Glucocerebrosidase (GBA1) gene mutations had been previously excluded. The patients mentioned above were followed in the Movement Disorders Outpatient clinic of Eginition Hospital, NKUA and have been enrolled in the ''Thalis'' database and biobank.

Demographic (age, sex, age at disease onset and disease duration) and basic clinical data [including motor disability grading with the Hoehn and Yahr Scale (H&Y), the pres-ence of motor complications and the Mini Mental State examination (MMSE score)] of these patients were retrieved. Moreover, treatment data (dopaminergic medication selec-tion, combination and dosage as well as the Levodopa Equivalent Daily Dose LEDD) were evaluated. The present study was conducted in agreement with the principles of the Dec-laration of Helsinki. Signed informed consent was obtained from all participants recruit-ed. The study was approved by the Scientific Board of Eginition hospital.

4. Results

Epidemiological and basic clinic data of PD carriers of pathogenic variants of recessive genes in our cohort are shown on Table 1. PRKN PD carriers (6M/7F) had an average age 50.4 ± 10.9, an average age at onset 37.6 ± 7.6 and disease duration was 14.3 ± 9.2 years. In PINK1 carriers (2M/1F) mean age was 64.7 ± 11.4, average age at onset 35 ± 3 and disease duration 29.7 ± 9.5 years. The H&Y score was relatively low even after decades of disease in carriers of both genes (2 ± 0.7 for PRKN carriers and 2.33 ± 0.58 for PINK1 carriers). Similarly, the MMSE score was excellent after many years of disease (29.54 ± 0.52 for PRKN and 27.33 ± 0.71 for PINK1 carriers). As far as the presence of motor complications is concerned, 9/13 of PRKN mutation carriers exhibited motor fluctuations and/or dyskinesias during their disease course. The same was true for 2/3 of PINK1 mutation carriers.

Table 1. Demographic and Basic Clinical data of PD patients carrying pathogenic or likely pathogenic variants in recessive PD-related genes.

	Age	Sex	Age at onset	Duration (years)	H & Y	Motor Complications	MMSE
PRKN 1	56	F	40	16	2	Absent	30
PRKN 2	67	F	47	20	3	Present	29
PRKN 3	41	F	29	12	1	Absent	30
PRKN 4	65	F	45	40	3	Present	30
PRKN 5	48	M	42	6	2	Present	29
PRKN 6	66	F	45	21	3	Absent	30
PRKN 7	48	M	40	8	1	Present	29
PRKN 8	40	F	32	8	2	Present	30
PRKN 9	35	M	29	6	1	Absent	29
PRKN 10 (Het)	57	F	44	13	2	Present	29
PRKN 11 (Het)	40	M	24	16	2	Present	29
PRKN 12(Het)	42	M	31	11	2	Present	30
PRKN 13(Het)	50	M	41	9	2	Present	30
PINK1 1	52	M	32	20	3	Absent	29
PINK1 2	74	F	35	39	2	Present	28
PINK1 3	68	M	38	30	2	Present	25

H&Y : Hoehn and Yahr Scale, MMSE : Mini Mental State Examination.

Regarding treatment, the average Levodopa Equivalent daily dose (LEDD) in PRKN carriers was 806.8 ± 453.5 (range 152-1810). Similarly, in PINK1 carriers the average LEDD was 765 ± 96.6 (range 660-850). Detailed treatment data for each participant are shown in Table 2. As far as therapeutic options are concerned, the majority of patients responded to low/moderate doses of Levodopa and

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were prone to the development of motor fluctuations and dyskinesias. Levodopa dosage lower than 400 mg/day was sufficient for 6/13 patients. Nevertheless, certain patients (3/16) could not tolerate even low Levodopa doses and alternative medication schemes like dopamine agonists and/or amantadine were selected. The response to Dopamine Agonists (DA) was often favorable both as initial and longitudinal therapy, although side effects occasionally arose (7/16 patients needed to discontinue or reduce the dosage of DA due to impulse control disorders or psychiatric manifestations). We have to underline the fact that 2/13 PRKN patients had clear-cut disabling psychotic features during their disease course and a third one manifested milder psychotic symptoms. All three had to receive antipsychotic treatment. In such cases psychosis occurred in the absence of dementia and is probably more linked to dopaminergic treatment especially dopaminergic agonists. It may manifest as an isolated delusional syndrome [29]. Psychotic symptoms or treatment were not reported among PINK1 carriers in our cohort.

Table 2. Treatment data of PD patients carrying pathogenic or likely pathogenic variants in recessive PD-related genes.

\	**Age**	**Sex**	**Duration (years)**	**LEDD**	**L-Dopa**	**COMT inhibitors**	**Dopa-Agonists**	**Rasagiline Amantadine**
PRKN 1	56	F	16	670	150mg	-	Ropinirole 6mg	400 mg
PRKN 2	67	F	20	1340	900mg	-	Rotigotine 8mg	200 mg
PRKN 3	41	F	12	320	-	-	Ropinirole 6 mg	200 mg
PRKN 4	65	F	40	793	250mg	Entacapone 1000mg	Ropinirole 8 mg	1mg 200 mg
PRKN 5	48	M	6	905	600mg	-	Pramipexole 1.05mg	200 mg
PRKN 6	66	F	21	320	-	-	Ropinirole 6mg	200 mg
PRKN 7	48	M	8	720	200mg	-	Rotigotine 4mg	400 mg
PRKN 8	40	F	8	1810	1600mg		Pramipexole 2.1mg	-
PRKN 9	35	M	6	660	200mg	-	Ropinirole 8 mg	1mg 200 mg
PRKN 10 (Het)	57	F	13	152	100mg	-	Pramipexole 0.52mg	-
PRKN 11 (Het)	40	M	16	833	350mg	Entacapone 600mg	-	1mg 300 mg
PRKN 12(Het)	42	M	11	705	600mg	-	Pramipexole 1.05mg	-
PRKN 13(Het)	50	M	9	1260	1050mg		Pramipexole 2.1mg	-
PINK1 1	52	M	20	660	-	-	Ropinirole 8 mg	1mg 400 mg
PINK1 2	74	F	39	785	500 mg	Entacapone 800mg	Rotigotine 4 mg	-
PINK1 3	68	M	30	850	750 mg	-	-	1 mg -

LEDD : Levodopa Equivalent Daily Dose; COMT : Catechol-O-methyltransferase.

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Rasagiline was also a useful add-on therapy (5/16). A very high number, 9/13 PRKN and 1/3 PINK1 carriers were treated with amantadine successfully, and this also applied to patients who could not tolerate Levodopa or DA. In some cases, amantadine had an especially good response in cases with bizarre gait patterns.

Due to the relatively mild symptomatology of patients in our cohort, there was no need for device-aided treatments [either an s.c. apomorphine / intestinal Levodopa-carbidopa gel pump or Deep brain stimulation (DBS)].

5. Discussion

The heterogeneity in the clinical features of PD has been elucidated thanks to large patient cohorts which have undergone deep phenotyping [2,7]. However, as far as treatment is concerned, the approach is uniform and predominantly symptomatic. Research evidence from targeted therapies for monogenic forms of PD aiming at neuroprotection may pave the way for new mechanism-based interventions for genetic PD forms and also for the more common idiopathic PD. An ameliorated stratification of patients might also support symptomatic treatments by predicting treatment efficacy and long-term adverse effects.

The clinical picture and course vary depending on the exact genetic cause and the specific mutation, but there is also a variability even within families with the same mutation [2]. The genetic diagnosis of the disease is important in these cases not only for genetic counseling and assessment of patient prognosis, but also because it can be taken into account for specific treatment options, including device-aided therapies [like Deep Brain Stimulation (DBS) or Levodopa-Carbidopa enteric gel pumps]. Furthermore, such patients could enroll in emerging neuroprotective clinical studies that are applied to specific genetic forms of the disease, in the context of pharmacogenomics [30]. With the gradual establishment of personalized treatment, the therapeutic approach in genetic PD forms might differ substantially as compared to idiopathic PD [31].

A very important issue to address is individual therapy optimization. Treatment with antiparkinsonian drugs is associated with the development of complications, such as Levodopa-induced fluctuations and dyskinesias, hallucinations and excessive daytime sleepiness. Carriers of specific genetic forms may be particularly susceptible to the development of some of these drug adverse effects. To our knowledge, there is a limited number of studies assessing dopaminergic medication schemes in cohorts of genetic PD patients carrying mutations in recessive genes. Although previous review articles on recessive PD genes provide information on treatment in such patients, real world data from clinical cohorts are sparse [32,33]. Most data derive from case reports or small case series. The majority of existing literature on precision treatment according to the genetic background has focused either on disease modifying treatments or device aided-therapies. Notably, more research has taken place regarding device aided treatments in patients with genetic PD that is not recessive [Glucocerebrosidase gene (GBA1) or Leucine-Rich Repeat Kinase 2 (LRRK2) carriers] [31].

A new study evaluated the impact of Levodopa-carbidopa intestinal gel infusion (LCIG) on 56 PD patients and genetic mutations were confirmed upon genetic testing in 9/56 (15%) [5 GBA1, 2 SNCA, 1 LRRK2, 1 PRKN]. Patients which underwent LCIG demonstrated an improvement of motor complications. This was also true for carriers of genetic mutations. No effect of the presence of pathogenic mutations regarding motor or cognitive functions could be observed [34].

In our cohort, lower LEDD doses were efficient even in patients with a very long disease duration, while certain patients were doing well without any Levodopa treatment decades after disease initiation. Other therapeutic options had been selected. DA can be used as a first and main line treatment regimen if well tolerated. Rasagiline was quite effective either as an initiation or an add-on therapy in patients with recessive PD forms. It furthermore appears that amantadine represents an attractive therapeutic option in PD with mutations in recessive genes, since it was generally effective and well tolerated. As we have pointed above, carriers of mutations in recessive genes in our cohort generally had a mild clinical course in terms of motor and cognitive function (low H&Y score and excellent MMSE score even after long disease duration). Moreover, our results on the absence of dementia are compatible with literature concerning PRKN and PINK1 mutations [2,7] although there are some exceptions notably for PINK1 carriers [35,36]. We should also mention the occurrence of psychotic symptoms in a minority of patients which can be isolated, triggered by

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dopamine agonists treatment and irrespective of general cognitive decline. According to our results, an impressive observation regarding treatment requirements is that a proportion of PD patients (3/13) carrying PRKN mutations had an excellent response to dopamine agonists and had not been started on L-Dopa therapy even after 20 years since disease onset. The lack of need for L-Dopa therapy supports the relatively benign nature of recessive genes-related PD [5].

Amantadine administered as monotherapy in early stages of PD produces a moderate improvement, which appears in a few days and concerns all the symptoms of the disease. Moreover, in advanced PD, amantadine has been shown to be effective in reducing dyskinesias based on its NMDA receptors blocking property. It is notable that in our cohort 10/16 patients were treated successfully with amantadine, providing evidence of its role in either early or advanced recessive gene related PD.

Furthermore, the lack of device-aided approaches in our cohort, might also be compatible with relatively low doses of L-Dopa overall, and the relatively benign nature of PRKN or PINK1 related PD even in terms of motor symptoms. However, a confounding factor is the difficulty of accessibility to DBS in Greece, which is the main device-aided therapy in young subjects. The latter may also be a contributing factor to the lack of such subjects in our cohort. Comparatively, in the review of Over and co-authors, 20 out of 1002 PD patients carrying PRKN mutation and 3 out of 151 PINK1 mutation carriers had undergone DBS [32].

According to previously published data, PD patients harboring PRKN mutations require low LEDD for an excellent control of motor signs, but despite receiving markedly low doses of Levodopa, they exhibited frequent development of motor complications and dyskinesias since early disease stages. Based on the previously mentioned features of PD patients carrying PRKN mutations, starting with a low LEDD and selecting dopaminergic agonist treatment rather than levodopa is recommended in the early stages [24,37]. However, in some studies, dopamine agonists are less effective on motor symptoms and do not delay the onset of motor fluctuations and dyskinesias compared to levodopa in the long run. Despite the absence of many other non-motor symptoms, neuropsychiatric disturbances are often present and severe in PRKN mutation carriers mainly, impulsive-compulsive behaviors [including gambling, compulsive buying, binge eating and sexual behaviors or excessive interest in hobbies [38]. Risk factors for therapy-related impulsive behavior include a novelty-seeker impulsive personality and the patient's demographic profile including young age, male sex, previous neuropsychiatric symptoms. These clinical characteristics should prompt for careful selection of dopaminergic therapy doses, as well as frequent monitoring for impulse-control disorders and behavioral disturbances. Bohlega and co-authors reported good motor and non-motor outcomes in a heterozygous PRKN mutation carrier with long follow-up [39], while Foltynie and co-authors describe two PRKN patients with compulsive behavior, but the outcomes were not specified [40].

We were able to largely replicate the observations of previous publications on recessive PD forms. A recent review evaluated the current landscape of treatments of monogenic PD forms including PRKN and PINK1 [32]. In this review study, 1002 PD patients harbored biallelic PRKN mutations and 54.2% were receiving L-Dopa (missing data ranged up to 45.3%). Mean duration of levodopa administration was 13 years. 94.5% were reported with good therapeutic outcome at an average dose of 490 mg/day (range: 100–2750). Another 6 patients were published with moderate improvement at, notably, lower levodopa dose (mean 100 mg/day), and 13 patients showed a rather poor response at a mean dose of 430 mg/day (range: 200–750). The response to L-dopa was irrelevant to the type of PRKN variant. In the same paper [32], 24.3% of patients receiving L-Dopa showed side effects with the levodopa therapy, including 124 with dyskinesia, 44 with motor fluctuations, 3 with levodopa-induced dystonia and 1 with hallucinations. 91 patients were treated with other non-levodopa medications including dopamine agonists, COMT inhibitors, MAO-B inhibitors, anticholinergics and/or amantadine. The impact of such therapy was mostly favorable. DBS brain surgery was reported in 20 Parkin mutation carriers, and a good clinical response was reported in all patients [32].

Regarding PINK1 in the same review [32], 151 patients with biallelic PINK1 mutations were assessed including 75.5% of carriers who were reported to receive levodopa therapy (no treatment information was available for 23.3%). The average duration of levodopa treatment was 13 years. The vast majority (n=93, 97.9%) showed a good outcome at a mean dose of 350 mg/day (range: 50–900)

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and 2 patients had minimal response at a higher mean dose of 1030mg/day. Adverse effects of the levodopa therapy were seen in 39.5% of patients including 40 mutation carriers with dyskinesia, 12 with motor fluctuations and 4 with dystonia. Regarding non-levodopa therapy options, 31 patients had been treated with dopamine agonists, COMT inhibitors, MAO-B inhibitors, anticholinergics, and/or amantadine. Clinical outcome was usually satisfactory. The reported response of 3 patients who underwent DBS was also favorable [32].

In the era of personalized treatment, the therapeutic approach in PD needs to be more targeted [32,33]. Genetic PD forms represent a novel field where precision medicine could be applied [37]. Recessive forms of PD in particular, share unique features and patients may benefit significantly from individualized treatments [20,37]. Better stratification strategies leading to precision medicine approaches pave the way for the improvement of symptomatic treatment and the ability to provide more patient-targeted care. Studies such as ours, focusing on the peculiarities of current pharmacological treatments in autosomal recessive genetic PD, may be useful to provide the framework upon which more specific disease-modifying therapies may be applied in the future.

Our single-center study adds to the body of evidence indicating that autosomal recessive PD due to PRKN or PINK1 mutations has a relatively benign nature and demonstrates a uniformly good therapeutic response to oral pharmacological treatment, despite prolonged disease duration. The study also provides evidence that treatment with amantadine may be particularly effective in this population. Lack of treatment with Levodopa 10 years or more after PD diagnosis in a relatively young patient should raise suspicion about the existence of autosomal recessive PD.

6. Conclusions

In the era of precision medicine and individualized treatment, the therapeutic approach in recessive PD gene carriers might differ as compared to idiopathic PD. Lower LEDD doses were efficient even in patients with a very long disease duration, while a few patients were doing well without any Levodopa treatment decades after disease initiation. DA could be used as a first and main line treatment regimen if well tolerated. It furthermore appears that amantadine represents an attractive therapeutic option in PD with mutations in recessive genes, since it was generally effective and well tolerated. Finally, according to literature data, in progressed disease stages most carriers of mutations in recessive PD genes have a favorable response to device-aided therapies.

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