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Levodopa Use and Long-Term Benefit in Different Dystonia Phenotypes

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ABSTRACT

Background: Dopaminergic changes have been reported in various forms of dystonia beyond dopa-responsive dystonia (DRD). Besides DRD, levodopa (LDopa) is generally not considered effective in dystonia and may worsen it. This study assesses the impact of LDopa on different dystonia phenotypes.

Objectives: The patient database of Tampere University Hospital was screened with data mining over a 5-year period to identify individuals with dystonia who had been prescribed LDopa and was evaluated for the possible long-term responsiveness of LDopa in different dystonia phenotypes.

Methods: The patient database was screened using data mining to identify dystonia patients associated with LDopa over a 5-year period. Clinical information and response to LDopa were evaluated.

Results: LDopa was considered beneficial with 32 of 71 patients. All DRD patients had long-term benefit of LDopa, as well as 44% generalized dystonia patients and 25% segmental dystonia patients, but none of the focal dystonia patients. Of the seven patients with functional dystonia, four considered LDopa originally beneficial, but the effect was temporary with two patients, resulting in elevating LDopa doses. LDopa benefit was associated positively with lower limb dystonia (OR 7.0, $p = 0.002$) and negatively with cervical dystonia (OR 0.2, $p = 0.001$). Moreover, long-term LDopa benefit had a significant correlation with unspecified stiffness (OR 4.0, $p = 0.014$) and walking difficulties (OR 3.8, $p = 0.022$).

Conclusions: Other than DRD, LDopa should only be considered in generalized dystonia patients with lower limb dystonia and walking difficulties. Objective estimation of symptoms should be conducted if considering LDopa treatment.

1 | Introduction

Dystonia is a movement disorder defined by muscle contractions causing abnormal postures, movements, and tremor [1]. In general, levodopa (LDopa) is not considered effective in dystonia and can exacerbate dystonic symptoms [2]. As an exception, dopa-responsive dystonia (DRD) is a heterogenous group of disorders defined by genetic changes leading to impaired dopamine synthesis in the brain. Several mutations have been recognized; the most known are autosomal dominant mutations in the guanosine triphosphate cyclohydrolase 1 (GCH1) gene and autosomal recessive mutations in the tyrosine hydroxylase (TH) or sepiapterin reductase (SPR) genes [3, 4]. DRD is treated with LDopa, which abolishes symptoms almost completely in most DRD patients.

On the other hand, dopaminergic changes have been reported in various forms of dystonia beyond DRD. Mild dopaminergic

dysfunction can occur in dystonia and parkinsonian features such as bradykinesia and rigidity have been reported in dystonia [5, 6]. Furthermore, some patients with parkinsonism-like extrapyramidal disease classified as scans without evidence of dopaminergic deficits (SWEDD) have been reported to possibly exhibit dystonia [7, 8]. The diagnosis of these patients is often unclear. LDopa could therefore be beneficial in reducing symptoms of these patients [9, 10]. The options for oral medication in dystonia are limited, and patients are often interested in the potential benefits of LDopa [11].

A trial of LDopa has been used as a diagnostic tool in younger patients presenting with DRD-like symptoms and lower limb dystonia [12]. However, this approach to symptom management has been criticized, as the benefits of LDopa may be difficult to measure in patients who experience only partial symptom relief. DRD is known to present with various phenotypes and is associated with multiple genetic backgrounds; therefore, genetic testing alone is not comprehensive [13]. Phenylalanine loading tests [14], urine pterin measurements [15, 16], and neurotransmitter metabolism analysis—such as homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), 3-methoxy-4-hydroxyphenylglycol (MHPG), and 3-O-methyldopa (3-OMD)—are generally recommended for the diagnosis of DRD [17].

We screened patient databases over a 5-year period to identify individuals who had been prescribed LDopa for different dystonic symptoms and evaluated the possible benefit of LDopa in different dystonia phenotypes.

2 | Methods

The Tampere University is a tertiary referral center in the Pirkanmaa wellfare county covering a total population of 900,000–1,000,000 people. The patient database of Tampere University Hospital was screened with data mining between January 1, 2018 and December 12, 2022 for patients who had ICD-10 diagnosis code G24.* or term “dystonia” in their patient records with co-occurrence of following terms: levodopa, Madopar, Kardopal, Sinemet, Stalevo, Duodopa, or Lecigon. The exclusion criteria for the study were previous diagnosis of Parkinson's disease or atypical parkinsonism, and lack of clinical information.

Clinical data were retrieved from the patient database. The following variables were collected from the medical records: sex, age at symptom onset, diagnosis, dystonia type, short- and long-term response to LDopa, maximum LDopa dose as LDopa equivalent (LE) dose, dopamine transporter imaging findings, results of genetic testing, and laboratory parameters.

Dystonia was categorized as focal, multifocal/segmental, generalized, DRD-like, or unspecified.

The LDopa dose was calculated as LE dose because of the frequent use of catechol-O-methyltransferase (COMT) inhibitors. The use of the COMT-inhibitor entacapone and opicapone was considered to increase the effective LDopa dose by 33% and 50%, respectively [18].

The presence of additional symptoms was recorded in a binary (yes/no) format, including disease progression, parkinsonism, ataxia, tremor, muscle cramps, cognitive impairment, fatigue, weakness, pain, walking difficulties, unspecified stiffness, oral motor symptoms, and dystonia in a first-degree relative.

The statistical analysis was done using SPSS Version 25.0. Kolmogorov–Smirnov test was used for normality test. Analysis of variance (Anova) was used for comparison of continuous variables with normal distribution, and Kruskal–Wallis test was used with variables without normal distribution. Chi square (χ^2) test was used for comparison between categorical variables.

Informed consent for patient information to be published in this article was not obtained because the Act on the Secondary Use of Health and Social Data in Finland (552/2019) permits the use of data created during health and social service sector activities for purposes other than the original reason for which it was collected. Informed patient consent was not necessary for this work.

3 | Results

Of the 90 retrieved patients, 71 were originally diagnosed with dystonia, 49 of whom were women. Their mean age was 29.1 ± 17.8 years, with no significant differences between the six diagnosis groups (Table 1). A total of 14 patients were excluded because dystonia was part of a previously diagnosed case of Parkinson's disease. Three patients were excluded because they did not present a dystonia phenotype. Two patients did not have clinical information available.

The final diagnoses of 71 patients were 9 focal dystonia, 8 segmental/multifocal dystonia, 19 generalized dystonia, 12 DRD, 7 functional dystonia, and 16 other disorders (Table 1).

The other disorders diagnosis group consisted of heterogenous patients: four who were originally considered having DRD phenotype (serine deficiency, central folate deficiency, and Coffin–Lowry syndrome [CLS] and genetically verified benign ataxia syndrome); one other metabolic disorder; two who were later diagnosed with Parkinson's disease with limb dystonia as preceding symptom; two dystonia-parkinsonism; and one who was later diagnosed with corticobasal syndrome (CBS). Six other patients did not have a definite diagnosis. These patients were included in the study because dystonia was considered the primary symptom.

DRD phenotype was considered if the patient had lower limb dystonia and walking difficulties without other explanation. Besides 12 DRD patients, DRD was originally suspected with two patients with functional dystonia and four above-mentioned patients in the other diagnosis group. One patient with a DRD-like phenotype in the other group did not have a diagnosis.

Unlike DRD patients, patients with generalized dystonia had more cervical (57.9%) and facial dystonia (47.4%) in addition to axial dystonia (Table 1).

TABLE 1 | The demographic data of study patients.

	Diagnosis (*n*)						
	Focal (9)	**Multifocal/ segmental (8)**	**Generalized (19)**	**DRD (12)**	**Functional (7)**	**Other (16)**	**All (71)**
Female	5 (55.6%)	6 (75%)	14 (73.7%)	8 (66.7%)	5 (71.4%)	11 (68.8%)	49 (69%)
Mean age of onset (years ± SD)	34.7 ± 10.1	40.4 ± 12.3	26.7 ± 15.4	21.4 ± 14.8	29.7 ± 11.5	28.1 ± 26.6	29.1 ± 17.8
Dystonia phenotype							
Focal	9 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (12.5%)	11 (15.5%)
Multifocal/ segmental	0 (0%)	8 (100%)	0 (0%)	0 (0%)	1 (14.3%)	5 (31.3%)	14 (19.7%)
Generalized	0 (0%)	0 (0%)	19 (100%)	1 (8.3%)	0 (0%)	2 (12.5%)	22 (31%)
DRD	0 (0%)	0 (0%)	0 (0%)	11 (91.7%)	2 (28.6%)	5 (31.3%)	18 (25.4%)
Unspecified	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (57.1%)	2 (12.5%)	6 (8.5%)
Dystonia location							
Facial dystonia	0 (0%)	2 (25%)	9 (47.4%)	0 (0%)	1 (14.3%)	2 (12.5%)	14 (19.7%)
Laryngeal dystonia	0 (0%)	0 (0%)	5 (26.3%)	0 (0%)	1 (14.3%)	0 (0%)	6 (8.5%)
Cervical dystonia	8 (88.9%)	6 (75%)	11 (57.9%)	1 (8.3%)	1 (14.3%)	1 (6.3%)	28 (39.4%)
Upper limb dystonia	1 (11.1%)	5 (62.5%)	19 (100%)	4 (33.3%)	5 (71.4%)	11 (68.8%)	45 (63.4%)
Lower limb dystonia	0 (0%)	2 (25%)	17 (89.5%)	12 (100%)	6 (85.7%)	13 (81.3%)	51 (71.8%)
Axial dystonia	0 (0%)	1 (12.5%)	19 (100%)	4 (33.3%)	2 (28.6%)	6 (37.5%)	32 (45.1%)

LDopa was originally considered beneficial with 43 patients (61%) without differences between genders. Of these patients, 32 (71%) had long-term benefit of LDopa. The loss of LDopa benefit was seen especially in the other diagnosis and functional dystonia groups (31% and 29% of patients, respectively) (Figure 1). The reasons to stop LDopa treatment were uncertainty of LDopa effect, side effects, or having another diagnosis.

The diagnosis group had significant correlation with long-term LDopa benefit ($p < 0.001$, χ^2). All DRD patients had long-term benefit of LDopa, as well as eight (44%) generalized dystonia patients, three (25%) segmental dystonia patients, two (29%) functional dystonia patients, and seven (44%) other patients (Figure 1). No focal dystonia patients had long-term LDopa benefit.

When comparing dystonia localization with long-term LDopa benefit, there was a significant positive correlation with lower limb dystonia (OR 7.0, CI 1.8–26.8, $p = 0.002$, χ^2) and a negative correlation with cervical dystonia (OR 0.2, CI 0.0–0.5, $p = 0.001$, χ^2) (Figure 2). Lower limb dystonia showed a significant positive correlation with LDopa even when the analysis was limited to non-DRD patients (OR 3.4, CI 1.1–2.3, $p = 0.027$, χ^2). LDopa benefit did not have a statistical effect in facial, laryngeal, axial, or upper limb dystonia.

Long-term LDopa benefit was associated significantly with unspecified stiffness (OR 4.0, CI 1.4–11.1, $p = 0.014$, χ^2), walking difficulties (OR 3.8, CI 1.3–11.3, $p = 0.022$, χ^2) and diurnal fluctuations (OR 5.6, CI 1.1–29.5, $p = 0.04$, χ^2)(Figure 3). No significant association was seen with other clinical manifestations.

Diagnosis groups differed significantly with their daily LE dose ($p = 0.002$, Kruskal–Wallis). DRD patients had the lowest median LE dose 207 mg (IQR 240 mg), and functional dystonia patients had the highest dose 772.5 mg (IQR 560 mg). Other groups had a median LE dose between 275 and 400 mg (Figure 4). In a post hoc multiple comparisons analysis, the LE dose in the functional dystonia group was significantly higher than in other groups.

The most reported benefits of LDopa were reduction of muscle cramps (25.4%), pain (11.3%), walking difficulties (9.9%), and stiffness (9.9%) (Table 2). There were no statistically significant differences between DRD and other patients in reported LDOPA benefits. No objective measurements of benefits were performed.

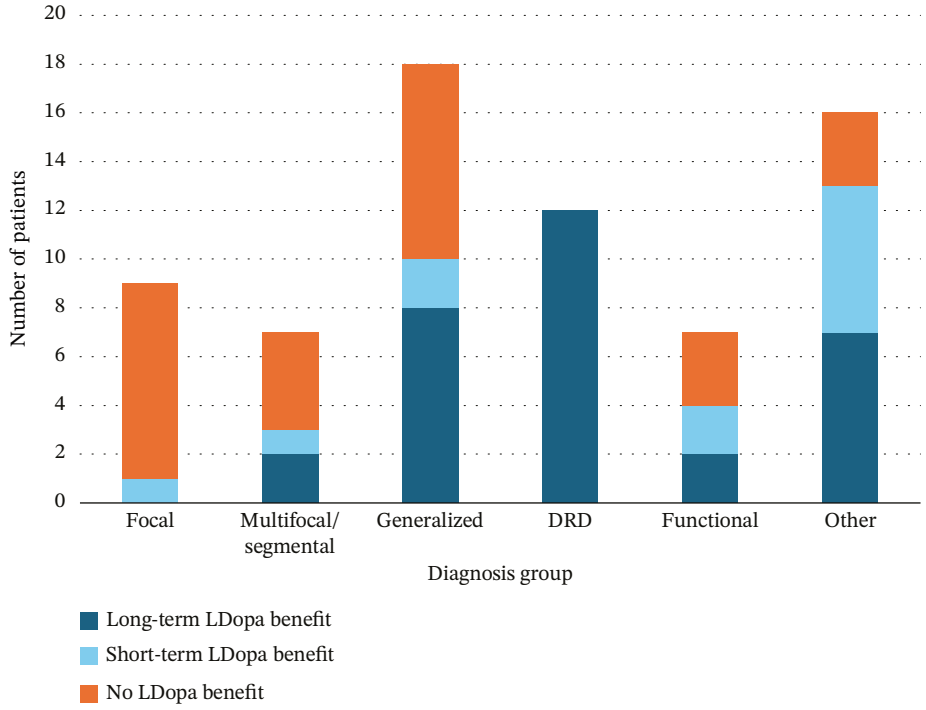

FIGURE 1 | A bar chart illustrating the number of patients with only short-term LDopa benefit, long-term LDopa benefit, and without any LDopa benefit across different dystonia subgroups.

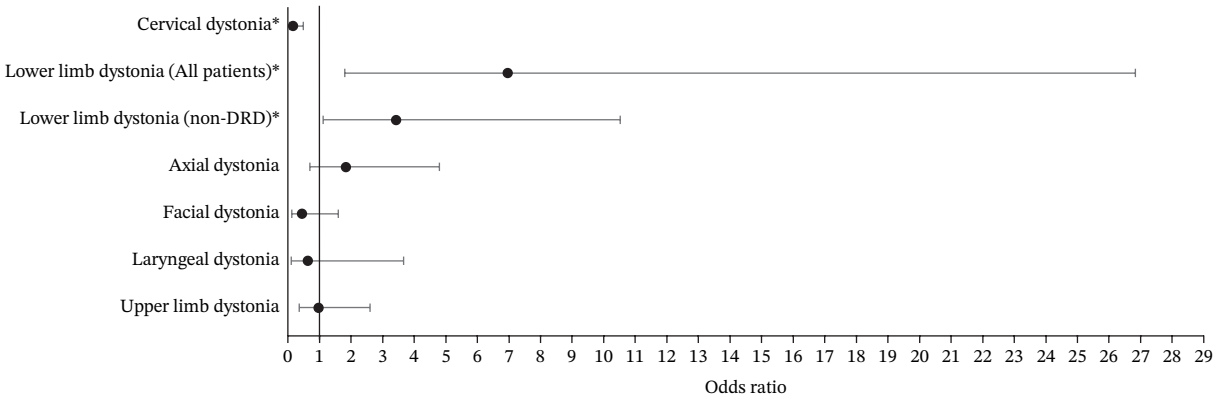

FIGURE 2 | Association between dystonia location and long-term LDopa benefit: forest plot illustrating odds ratios and 95% confidence intervals. $* p$ value < 0.05.

Most reported side effects of LDopa were fatigue (5.6%), walking difficulties (4.2%), and nausea (4.2%) (Table 3).

Dopamine transporter imaging was performed on 21 patients. Three of them showed slight abnormalities, two had focal limb dystonia and were subsequently diagnosed with Parkinson's disease, and one had a progressive condition with suspected atypical parkinsonism.

Gene studies were done on 20 patients: 4 patients had single gene studies, 4 patients had gene panel testing, and 10 had whole exome sequencing.

Two of 12 DRD-patients were discovered with significant gene mutations: compound heterozygous GCH1-mutation and compound heterozygous PTS mutation. One patient with suspected DRD was later found to have NKX2-1 gene mutation, thus diagnosed with benign hereditary ataxia, and another one was found to have compound heterozygous RPS6KA3 mutation causing CLS, with lower limb dystonia responsive to LDopa. One adult-onset generalized dystonia patient without LDopa benefit had GNAL-gene mutation. Another generalized dystonia patient with long-term LDopa benefit was found to have mutations of uncertain significance in FUS and STXBP5L genes. One segmental dystonia patient without long-term LDopa benefit had a mutation of uncertain significance in the ZNF710C gene. A dystonia–parkinsonism patient with long-term LDopa benefit was found to have likely significant heterozygous mutation in PLA2G6-gene.

Cerebrospinal fluid amino acid and neurotransmitter measurements were performed with 11 patients, three of them with DRD

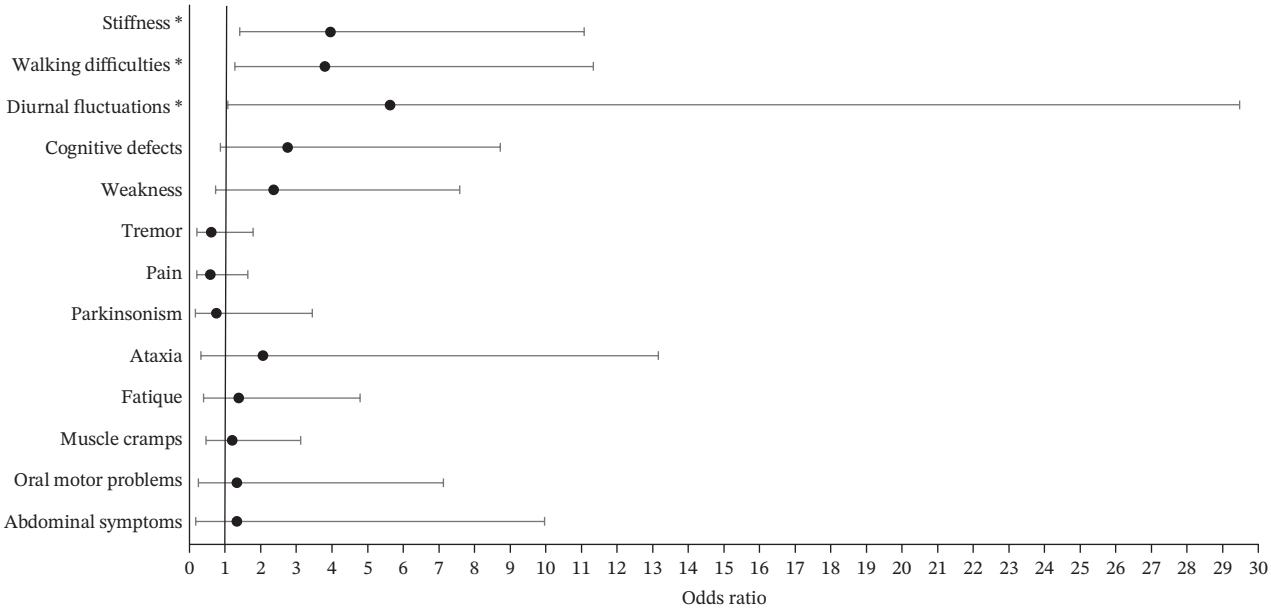

FIGURE 3 | Association between various clinical manifestations and long-term LDopa benefit: forest plot illustrating odds ratios and 95% confidence. $* p$ value < 0.05.

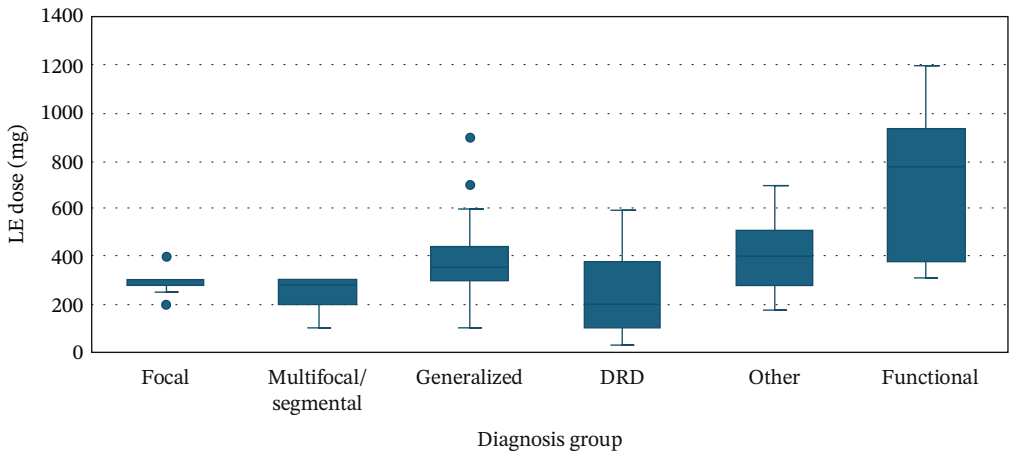

FIGURE 4 | Levodopa equivalent dose across different dystonia subgroups. Median values are indicated by horizontal lines. Boxes represent the interquartile range (IQR), and whiskers extend to 1.5×IQR. Outliers are denoted by individual dots.

diagnosis. With one patient, the newborn screen revealed high plasma phenylalanine content leading to diagnosis of tetrahydrobiopterin (BH4) deficiency. Two DRD patients did not have biochemical alterations leading to diagnosis. Another patient in the other diagnosis group had metabolic changes related to central pyridoxine and folate deficiency.

4 | Discussion

The long-term benefit of LDopa varied considerably between different dystonia groups. Besides DRD patients, generalized dystonia patients were most likely to benefit from LDopa use. Patients with focal dystonia did not benefit from LDopa. The only patient with a focal dystonia phenotype who responded to LDopa was later diagnosed with Parkinson's disease, as was a patient with segmental dystonia phenotype with limb dystonia. Another patient with focal limb dystonia, who did not respond to LDopa, was later diagnosed with CBS. Dopamine transporter imaging should be considered with adult-onset limb dystonia patients, because of the risk of progression to Parkinson's disease or atypical parkinsonism [19].

The diagnosis of DRD was challenging in many cases. Two functional patients and four patients in the other diseases group were considered to have DRD-phenotype. The typical phenotype of DRD consists of childhood or adult–onset lower limb dystonia with walking difficulties and diurnal fluctuations, with worsening of symptoms during the day [20]. However, the disease phenotype varies even in genetically verified DRD [21–23]. In DRD-plus syndromes, patients may have other atypical symptoms, like cognitive delay, seizures, or other neurological manifestations, besides DRD features [24].

TABLE 2 | Symptoms relieved with LDopa ($n = 71$).

	n(%)
Muscle cramps	18 (25.4%)
Pain	8 (11.3%)
Walking difficulties	7 (9.9%)
Stiffness	7 (9.9%)
Muscle weakness	5 (7%)
Fatigue	3 (4.2%)
Dystonia	3 (4.2%)
Cognition	2 (2.8%)
Tremor	1 (1.4%)
Mood	1 (1.4%)
Hypokinesia	1 (1.4%)
Aphasia	1 (1.4%)

TABLE 3 | Side effects caused by LDopa ($n = 71$).

	n(%)
Fatigue	4 (5.6%)
Walking difficulties	3 (4.2%)
Nausea	3 (4.2%)
Hallucination	2 (2.8%)
Stiffness	2 (2.8%)
Tremor	2 (2.8%)
Dyskinesia	1 (1.4%)
Dystonia	1 (1.4%)
Erytrodermia	1 (1.4%)
Muscle cramps	1 (1.4%)
Polyneuropathy	1 (1.4%)
Balance	1 (1.4%)
Insomnia	1 (1.4%)
Gastrointestinal symptoms	1 (1.4%)

Eleven patients had neurotransmitter measurements. The only DRD patient with confirmed neurotransmitter changes was a newborn baby with high plasma phenylalanine in routine screening without a typical phenotype. Genetic testing of various levels was done on 20 patients, six of them leading to diagnosis, confirming the DRD diagnosis with two patients. Even without confirmed metabolic changes or genetic alterations, DRD was considered the most likely diagnosis based on typical phenotype and good LDopa response with 10 other patients, who continued using LDopa.

In DRD, an almost complete resolution of symptoms has been considered as a diagnostic marker [25]. In this study, 61% of the study population reported a subjective benefit at the beginning of treatment. However, long-term benefit was observed by only 45%, demonstrating that initial subjective improvement with LDopa may not predict a sustained therapeutic effect. It is likely that most of the initial benefit is due to a placebo effect, which is a prominent factor in the treatment of neurological diseases [26, 27].

Four patients with subsequent functional dystonia diagnosis considered LDopa beneficial originally. The functional dystonia patients had also significantly higher LE dose. These patients may have experienced a temporary subjective effect of LDopa, resulting in a gradual increase in the total LE dose. However, this could potentially lead to an increase in side effects. In two patients, the symptoms were relieved after gradual discontinuation of LDopa. Augmentation, defined as a treatment-related increase in symptom severity, is a common risk associated with LDopa use in RLS [28]. The etiology of the symptom is not known, but D2-receptor hyperactivation and low ferritin levels have been associated with it [29, 30]. A similar mechanism of augmentation could be behind the worsening of the symptoms with functional dystonia patients with high LDopa doses.

Lower limb dystonia was significantly associated with a positive long-term response to LDopa, as well as a lack of cervical dystonia, which might reflect the cervical dominance in focal dystonia. The lower limb association with LDopa prevailed even when the DRD patients were excluded from the analysis. The patients with other dystonia locations did not have a long-term LDopa effect.

In this study, diffuse symptoms, like unspecified muscle stiffness, pain and walking difficulties without clear dystonia, or parkinsonism, were reported to benefit from LDopa. The nature of subjective stiffness was neither described in the patient records, nor was it clearly associated with dystonic posture, rigidity, or spasticity. Walking difficulties usually were reported to relieve because of LDopa treatment, but objective measurements were generally not done, and mostly subjective benefit was recorded. Only three patients considered LDopa relieving dystonia itself. It is likely that some of the reported improvements, particularly in muscle cramps and walking difficulties, are due to the direct relief of dystonia. However, other mechanisms may also contribute, such as parkinsonism, as no clear improvement in dystonic postures was documented, and the reported stiffness and walking difficulties were not classified in the patient records. One patient reported that LDopa worsened his dystonia.

Only one patient was reported to have LDopa-induced dyskinesia as a side effect. This is in line with previous reports, where dyskinesia is rare in DRD [31]. The most common side effect was fatigue. Curiously, walking difficulties as a side effect were also reported with three patients, even though improvement of walking correlated with the positive LDopa effect in these three patients.

Besides DRD, LDopa should only be considered in generalized dystonia patients with lower limb dystonia and walking difficulties. Because many of the symptoms and the effect of LDopa are difficult to evaluate objectively during outpatient visits, it is

recommended that symptom assessment be conducted through systematic long-term follow-up and physiotherapeutic evaluation when considering LDopa treatment. A systematic approach to evaluate dystonia using well-documented rating scales should be used, for example Global Dystonia Severity Rating Scale (GDS) or Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS). Also, genetic screening and metabolic testing should be considered systematically if DRD is suspected or LDopa treatment is considered. If the LDopa dose increases substantially, the diagnosis should be re-evaluated.

Author Contributions

Rebekka M. Ortiz: conception, organization, execution, design, execution, and writing of the first draft. Jari Honkaniemi: conception, review, and critique.

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Disclosure

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Ethics Statement

All procedures were performed in compliance with relevant laws and institutional guidelines and have been approved by the Wellbeing Services County of Pirkanmaa. Ethical approval was not sought because permission for this study was obtained from the Wellbeing Services of Pirkanmaa (R23563; § 33/2023). Informed consent for patient information to be published in this article was not obtained because the Act on the Secondary Use of Health and Social Data in Finland (552/2019) permits the use of data created during health and social service sector activities for purposes other than the original reason for which it was collected. Informed patient consent was not necessary for this work. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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