Movement Disorders
CLINICAL PRACTICE
REVIEW

Movement Disorders in Autosomal Dominant Cerebellar Ataxias: A Systematic Review

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Abstract: Autosomal dominant cerebellar ataxias (ADCAs) are clinically heterogeneous disorders classified according to genetic subtype and collectively known as SCAs. In a few SCAs, movement disorders can be the most frequent extracerebellar sign. The aim of this article is to perform a systematic review of movement disorders frequency and characteristics in ADCAs. This work consisted of a structured search of electronic databases up to January 2013. Publications containing descriptions of ADCA clinical features written in several languages were selected initially based on title and abstract screening, followed by full-text reading of potentially relevant publications. Clinical findings and demographic data on genetically confirmed patients were extracted. Analysis of individual patient data from subjects with movement disorders was performed using the chi-square test and logistic regression. One thousand and sixty-six publications reviewing 12,151 patients from 30 different SCAs were analyzed. Individual data were available from 755 patients with at least one type of movement disorder during overall disease course. Of 422 patients in whom onset symptom data were available, one third referred a movement disorder as the initial symptom. During overall disease course, parkinsonism was common in many SCA subtypes, frequently described in the absence of ataxia and characterized as responding to dopaminergic medications. Motor complications developed occasionally in some patients as did nigrostriatal imaging alterations. Other frequent features were dystonia, chorea, and myoclonus. Rare conditions, such as akathisia, paroxysmal nonkinesigenic dyskinesia, or stiff person-like syndrome, were also reported. ADCA descriptions included a full range of movement disorders. Aside from postural or intention tremor, dopamine-responsive parkinsonism and dystonia were the most common.

Autosomal dominant cerebellar ataxias (ADCAs), genetically defined as SCAs are clinically heterogeneous neurodegenerative disorders, characterized by progressive ataxia presenting alone or in combination with other neurological features. Only on rare occasions is ataxia absent. Genetic abnormalities are variable and include repeat expansions in coding and noncoding regions of genes, conventional mutations, or large gene rearrangements, explaining, in part, clinical manifestation heterogeneity as well as differences in age of onset, disease severity, and progression.[1]

Movement disorders are among the most common noncerebellar symptoms of ADCAs and include both hypo- and hyperkinetic manifestations, such as parkinsonism, dystonia, chorea, and myoclonus, among others.[2] In some SCA subtypes, movement disorders are the predominant clinical expression, whereas in others they can be the sole manifestation or the only presenting feature. This makes presumptive ADCA diagnosis during initial stages a real challenge because it may resemble its idiopathic counterparts (e.g., Parkinson's disease [PD] or Huntington's disease [HD]).[3–5] Diagnosis becomes even more difficult when patients show nigrostriatal pathway disruption on functional neuroimaging,[6,7] or partial or complete response to dopamine replacement therapy (DRT),[5,8]or develop dopaminergic-related motor complications, such as motor fluctuations and dyskinesias.[9]

A previous review described many types of movement disorders present in ADCAs, linking them to the most probable SCA subtype, in particular, cases when ataxia was associated with a given movement disorder.[10] We aim to report the frequency and characteristics of movement disorders and analyze individual

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patient data to explore different characteristics of the most common movement disorders, such as parkinsonism and dystonia and their relationship to medication or ataxia. Also, to describe infrequent phenomenology or conditions, such as head tremor, myokymia, restless legs syndrome (RLS), tics, akathisia, paroxysmal nonkinesigenic dyskinesia (PNKD), stiff person-like syndrome, stuttering, spasmodic-like dysphonia, laryngeal stridor, and palatal tremor (myoclonus), albeit present in many types of ADCAs, which have received scarce attention in the medical literature.

Methods

Details of the search strategy, selection of studies, data extraction, and statistical analysis of the systematic review that served as the source of the present analysis were published elsewhere.[11] In brief, a comprehensive systematic search of electronic databases up to January 2013 was undertaken to include original articles, clinical notes, case reports, letters, congress abstracts, or any other publications potentially containing phenomenological descriptions or proportions of ADCAs published in English, Spanish, French, German, Italian, or Portuguese. Some researchers were contacted to identify gray literature. Back-searching of retrieved publication reference lists was conducted to scan for other relevant publications missed by the structured search. Selection of studies was based on a two-step sequence: First, potentially relevant publications were identified after title and abstract screening. If no abstract was available, a publication could still be selected during the second step, in which full-text reading was undertaken to identify clinical feature descriptions or rate reporting. Data were extracted only for patients with genetic SCA confirmation. Presence or absence of clinical features was recorded in a standardized data sheet only when explicitly mentioned in the text and extracted exactly as described (e.g., unspecific descriptions, such as extrapyramidal or dyskinesia). When possible, individual patient data were extracted, including demographics, clinical features, medication use, or complementary studies. Patients with drug-induced movement disorders were excluded.

Descriptive data were presented as mean ± standard error of the mean or proportions. Categorical variables were analyzed by chi-square test with Yates' correction and logistic regression. If overall $P < 0.01$, pair-wise comparisons were done by chi-square test. IBM SPSS software (version 20; SPSS, Inc., Chicago, IL) was used for statistical analysis.

Results

Eleven thousand one hundred and fifty-two publications were screened during this literature search. A flow diagram shows the disposition of publications that the search yielded was reported

TABLE 1 Movement disorders found at disease onset of different SCA subtypes

SCA Type	Intention or Postural Upper-Limb Tremor	Head Tremor	Parkinsonism	Chorea	Myoclonus	Dystonia
SCA1						1/244
SCA2	8/1007	12/1007	53/1007		1/1007	7/1007
SCA3	3/603		28/606			8/603
SCA4						
SCA5						
SCA6	1/544		9/545			6/544
SCA7	4/286					1/286
SCA8	17/71					1/71
SCA10						
SCA11	1/24					
SCA12	74/114					1/114
SCA13						
SCA14	8/100				8/100	1/100
SCA15-16	9/65				1/10	
SCA17	2/126		15/126	7/126		6/126
SCA18						
SCA19-22						
SCA20	1/14					
SCA21						
SCA23	1/10	1/10				
SCA25						
SCA26						
SCA27	14/19					
SCA28						
SCA29						
SCA30						
SCA31	2/258					
SCA35						
SCA36						
DRPLA	5/171			12/171	3/171	3/171
Total (%)	150/3945 (3.8)	13/3945 (0.3)	105/3945 (2.6)	19/3945 (0.5)	13/3945 (0.3)	35/3945 (0.9)

DRPLA, dentatorubro-pallidoluysian atrophy; NOS, not otherwise specified.

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TABLE 2 Frequencies of movement disorders at disease onset based on patients with individual data

Total No. of Patients	422 (100%)*
Patients with ataxia as presenting symptom	159 (38%)
Patients with a movement disorder as presenting symptom	123 (29%)
Parkinsonism	78
Dystonia	20
Postural or intention upper-limb tremor	10
Head tremor	6
Chorea	5
Myoclonus	4
Akathisia	1
Patients with ataxia plus any movement disorder at disease onset	18 (4%)
Dystonia	7
Chorea	5
Head tremor	2
Parkinsonism	1
Myoclonus	1
Postural or intention upper-limb tremor	1
Restless legs syndrome	1
Patients with ataxia plus any other neurological feature	35 (8%)
Patients only with neurological features other than ataxia or movement disorders as initial symptom	87 (21%)

*Total percentages are not always 100%, because some patients began with more than one type of movement disorder.

elsewhere.[11] Clinical features from 12,151 genetically confirmed patients among 30 SCA subtypes were extracted. Patients with movement disorders that were reported with individual data at disease onset and overall disease were available for 422 and 755 patients, respectively. Four patients with exposure to typical antipsychotic medication were excluded.

Movement Disorders at Disease Onset

Movement disorders found at disease onset of different genetically confirmed SCA subtypes are described in Table 1. Prevalence for all types of movement disorders at disease onset was inferior to 4%. Frequencies of movement disorders at disease onset based on individual data are shown in Table 2. In all, approximately 30% of patients began with a movement disorder, whether isolated or in combination with ataxia. Logistic regression, including age, gender, and main movement disorders as independent variables, disclosed that age at onset ≥34 years was, as an independent factor, related to the presence of parkinsonism (odds ratio [OR]: 2.14; 95% confidence interval [CI]: 1.23–3.72), chorea (OR, 2.15; 95% CI: 1.11–4.16), and myoclonus (OR, 0.35; 95% CI: 0.17–0.71).

Movement Disorders During Overall Disease Course

The most common movement disorders found during overall disease course of different genetically confirmed SCA subtypes are described in Table 3. Uncommon movement disorders were described in rare cases, such as PNKD (SCA 27), tics (SCA17, SCA25, and DRPLA), stuttering and akathisia (SCA3), palatal tremor or myoclonus and spasmodic-like dysphonia (SCA20), and stiff person-like syndrome (SCA1 and SCA3).

Figure 1 shows the relationship between the most frequent types of movement disorders present alone or in combination with other symptoms during overall disease course of patients with individual data. In all, 491 of 755 (65%) patients had a single movement disorder, whereas 264 (35%) showed two or more movement disorders combined. The most frequent combinations were parkinsonism plus dystonia (35%), chorea plus myoclonus (11%), chorea plus dystonia (9%), dystonia plus myoclonus (5%), and parkinsonism plus chorea (4%), followed by other less-common combinations.

Dystonia

Table 4 shows the frequencies of dystonic features of patients with individual data during overall disease course. In 9 of 140 patients (6%), botulinum toxin (BoT) use was reported, with a partial response observed in all. Dopamine replacement therapy (DRT) was also tried in 16 of 140 patients (11%), with partial response in 75% of the cases.

Parkinsonism

Parkinsonism was the movement disorder most frequently described in absence of ataxia during overall disease course ($P = 0.01$). However, of those "pure" parkinsonian patients, 30% exhibited cerebellar or brainstem atrophy on MRI. DRT use was reported in only half of the parkinsonian patients. When levodopa was used, mean daily dose was 572 ± 78 mg. In cases with parkinsonism, either alone or in combination with ataxia, response to DRT was inversely related to the presence of ataxia ($P = 0.001$; OR, 0.25; 95% CI: 0.07–0.72). Parkinsonism during overall disease duration responded to DRT in 107 of 138 (78%) patients described. Motor complications were described in a few of those patients (dyskinesias in 25 [23%] patients and motor fluctuations in 21 [20%]).

Functional Imaging of Parkinsonism

Dopaminergic imaging to evaluate nigrostriatal pre- and postsynaptic integrity was performed either with single-photon emission CT (99mTc-TRODAT-1, [123]I-FP-CIT or [123]I-IBZM) or PET ([18F]-dopa or [11C]-raclopride) in 52 of 271 (19%) patients with parkinsonism, of which 47 (90%) showed alterations. Some patients underwent only presynaptic evaluation with radioligands, such as 99mTc-TRODAT-1, [123]I-FP-CIT, or PET [18F]-dopa, whereas others included also postsynaptic functional imaging studies, such as [123] I-IBZM or [11C]-raclopride. Presynaptic involvement was found in 47 of 52 (90%) patients, whereas postsynaptic alterations were described in all 18 patients evaluated. In some cases, basal ganglia nuclei involvement was reported, corresponding to the putamen in 27 of 28 (96%) patients and to the caudate in 25 of 28 (89%). Asymmetrical alterations were present in 26 of 43 (60%) of the cases. Eight patients with ataxia without

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TABLE 3 Most common movement disorders rates of SCA subtypes during overall disease course*

SCA Type	Intention or Postural Upper-Limb Tremor	Head Tremor	Parkinsonism			Chorea	Myoclonus	Dystonia	Myokymia	Restless Legs	Extrapyramidal Signs or Parkinsonism (NOS)
			Bradykinesia	Rigidity	Rest Tremor						
SCA1	123/277	1/1	11/78	15/233	12/205	24/345	15/256	47/394	8/62	4/23	47/330
SCA2	322/646	76/177	100/258	97/408	85/356	52/568	84/451	127/862	9/317	9/43	34/233
SCA3	82/280	2/4	179/737	176/1036	51/504	37/689	43/580	442/1825		95/252	108/672
SCA4											
SCA5	6/16	1/1			2/15			2/7	5/22		0/7
SCA6	52/259	1/1	9/227	23/444	7/173	5/341	4/363	19/452		4/15	9/177
SCA7	39/111	1/8	1/47	5/39		12/87	6/32	23/131	14/89	7/17	31/184
SCA8	32/52		3/21	2/16	1/15	0/1	8/37	3/3			0/21
SCA10	9/16		2/2	1/1		0/27	0/27	1/28			0/76
SCA11	0/3										1/21
SCA12	77/115	2/4	9/10					2/16	2/6		0/1
SCA13			1/8					1/8			
SCA14	6/10	7/33	1/19	3/42	0/13	2/14	13/87	10/49	6/30	1/8	0/6
SCA15-16	27/46	3/9				2/10	2/13		2/10		2/23
SCA17	11/25	1/4	17/22	54/68	4/20	40/83	4/15	58/110			24/60
SCA18		2/7									
SCA19-22	2/10						2/19				0/9
SCA20		2/14	7/13								
SCA21			12/16	5/16	10/16						
SCA23	3/4	2/4									
SCA25	1/6	1/6							1/6		
SCA26											
SCA27	14/18	7/16				10/17					0/1
SCA28	1/11	1/24						3/24			3/24
SCA29								1/20			
SCA30	0/6		1/6				0/6				
SCA31	7/65		0/2	0/34	0/2			1/42			11/146
SCA35	5/12							4/11			
SCA36	2/44	1/44					1/44				0/14
DRPLA	24/53	3/3	4/10	1/2	1/2	137/215	78/179	36/103			5/13
Total (%)	845/2100 (40)	114/360 (32)	356/1475 (24)	364/2320 (16)	165/1311 (13)	321/2397 (13)	260/2109 (12)	780/4085 (19)	131/558 (24)	120/358 (33)	276/2025 (14)

*Adapted from Rossi et al.[11]
DRPLA, dentatorubro-pallidoluysian atrophy; NOS, not otherwise specified.

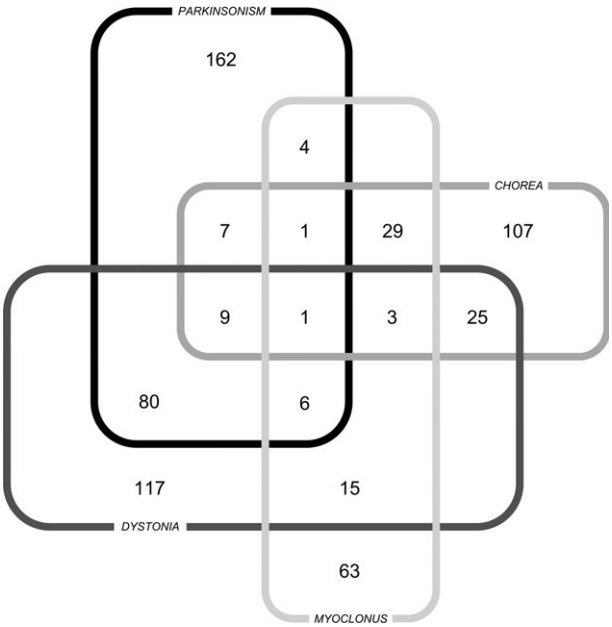

Figure 1 Number of patients with individual data of movement disorders during overall disease course.

TABLE 4 Frequencies of dystonic features of patients with individual data during overall disease course

Total No. of Patients	140 (%)*
Upper-limb dystonia	66/140 (47%)
Writer's cramp	8/66 (12%)
Lower-limb dystonia	31/140 (22%)
Cervical dystonia	42/140 (30%)
Blepharospasm	10/140 (7%)
Craniofacial dystonia	5/140 (4%)
Lingual dystonia	3/140 (2%)
Dystonia NOS	116

*Percentages are not always 100%, because some patients had more than one type of movement disorder. NOS, not otherwise specified.

parkinsonism, 1 with myoclonus and 2 with dystonia, underwent dopaminergic imaging tests. Symmetric alterations were described in 6 (75%).

Discussion

This systematic review assessed the frequencies and characteristics of varied types of movement disorders in several genetic SCA subtypes. In almost one third of patients on whom individual data were available, movement disorder was the initial symptom. After intention or postural upper-limb tremor, which can also form part of cerebellar syndrome, parkinsonism was the most frequent movement disorder at onset, followed by dystonia. Certain movement disorders were typically present at onset, in particular, SCA subtypes, as was the case of myoclonus in SCA14, parkinsonism in SCA17, and intention or postural upper-limb tremor in SCA8, SCA12, SCA15-16, and SCA27.

During overall disease, parkinsonism continued to be the most common movement disorder, followed in descending order by dystonia, chorea, myoclonus, myokymia, RLS, and head tremor. As had been observed for disease onset, during the course of the disease, some genetic subtypes had significantly higher proportion of a particular movement disorder, compared with the rest, such as parkinsonism, myokymia, intention or postural upper-limb tremor and head tremor in SCA2, dystonia in SCA3, intention or postural upper-limb tremor in SCA12, parkinsonism, chorea, and dystonia in SCA17, parkinsonism in SCA21, chorea in SCA27, and the combination of chorea, myoclonus, and dystonia in DRPLA11. A diagnostic scheme for movement disorders typically present at onset or during overall disease course in particular SCAs subtypes is depicted in Figure 2.

Intention or postural tremor was described in almost all SCA subtypes. Presence of L-dopa-responsive intention or postural tremor in young patients, associated with orthostatic tremor with a frequency range of 14 to 18 Hz, was described in SCA3.[12]

Rigidity and bradykinesia were the most frequent isolated parkinsonian signs, followed by rest tremor. Patients with isolated parkinsonism often developed ataxia during the course of disease. However, few presented parkinsonism without ataxia, even after 30 years of follow-up.[3,8,13] Many parkinsonian patients descriptions resembled those of idiopathic PD (iPD) patients, sharing clinical features, such as asymmetric onset, late age at onset, slow progression, and good response to DRT.[3,13–18] However, one third of patients with isolated parkinsonism exhibited cerebellar or brainstem atrophy on MRI. Screening for SCA mutations in patients with parkinsonism without a cerebellar syndrome is not recommended, except for SCA2 (especially in Asian ethnic groups) and SCA17 in families with autosomal dominant parkinsonism.

DRT use was reported in only half the parkinsonian patients on whom individual data were available. Both complete and partial responses were observed of magnitude inversely related to the presence of ataxia. SCA patients with parkinsonism resembling iPD were commonly responsive to DRT.[5,8] Dopaminergic-related motor complications, such as motor fluctuations and dyskinesias, were also described.[5,9,13]

Dopaminergic functional imaging with SPECT (99mTc-TRODAT-1, [123]I-FP-CIT, or [123]I-IBZM) or PET ([18F]-dopa or [11C]-raclopride) was seldom performed in SCA patients with parkinsonism. Pre- and postsynaptic alterations of the nigrostriatal pathway were found. Asymmetric findings, such as those observed in iPD,[18,19] were common, though almost uniform affectation of putamen and caudate was found in most cases, distinguishing these patients from iPD cases, which tend to show predominant putamen involvement. Affectation of nigrostriatal pathway integrity might help explain the presence of dopamine-responsive parkinsonism and occasional development of motor fluctuations or dyskinesias. However, the presence of presynaptic alteration on dopaminergic functional imaging and response to DRT are both findings for which further clarification is needed. Although rare, simultaneous iPD cannot be ruled out in the cases described. Recently, sequence variations of the glucocerebrosidase gene, which have been

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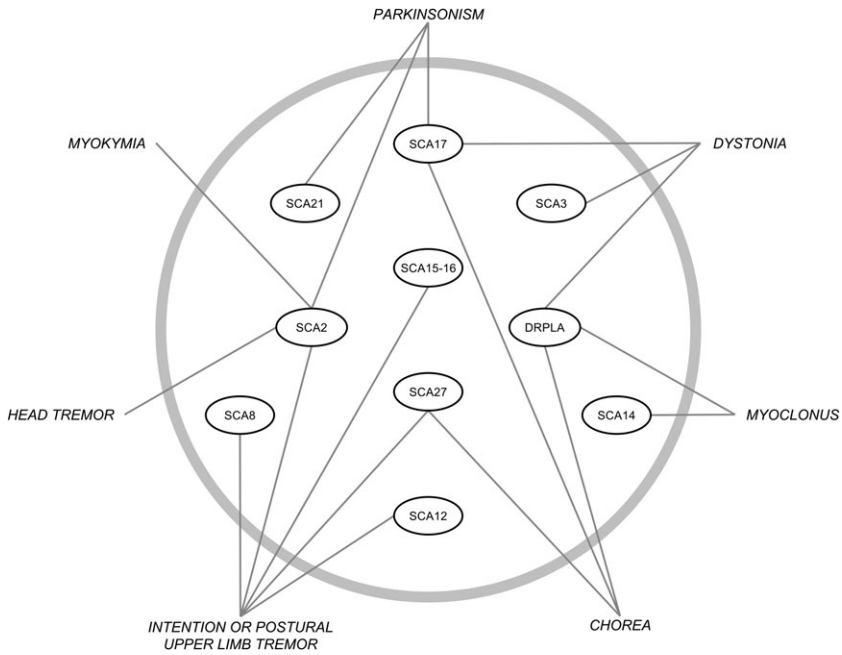

Figure 2 Diagnostic scheme for movement disorders typically present at onset or during overall disease course in particular SCA subtypes.

associated with iPD, were found in some SCA3 parkinsonian patients.[20] Interestingly, symmetric nigrostriatal pathway disruption was also observed in some ataxic patients without parkinsonism.[6,7] Similarly, SN hyperechogenicity was frequently observed in ADCA patients, even those without movement disorders.[21]

Dystonia was the third-most commonly described movement disorder during overall disease, whether in focal, segmental, or even generalized form.[2,10] Presence of dystonia strongly suggested diagnosis of SCA3, SCA17, and dentatorubral-pallidoluysian atrophy (DRPLA).[11] However, few SCA2 patients with cervical dystonia were also reported, which can be as frequent as 61% in some series.[22] Upper-limb involvement was present in almost half of the dystonic patients described, including writer's cramp. Other dystonic features reported were, in descending order, cervical dystonia, lower-limb dystonia, blepharospasm, apraxia of eyelid opening, and craniofacial and lingual dystonia. In a few cases, DRT was tried, usually with partial response; seldom were responses marked.[23–25] The most effective therapy was BoT, but, surprisingly, its use was rarely reported.[26,27]

Chorea was frequently associated with SCA17, SCA27, and DRPLA, and, in several cases, phenotype was indistinguishable from HD.[4,11,28] Myoclonus was observed often in SCA14 and DRPLA and rarely in other SCA subtypes.[11] This could be of cortical, brainstem, or spinal origin and usually showed a poor response to different pharmacological treatments.[29,30] RLS was reported in six SCA subtypes with an overall frequency of 33%, which is superior to the 5% to 15% found in the general population.[31] RLS rates increased with age and were mostly independent from peripheral neuropathy. This suggests a central origin, possibly resulting from dopaminergic dysfunction, also supported by the response to L-dopa.[32,33]

Less commonly reported were paroxysmal nonkinesigenic dyskinesia, stiff person-like syndrome, akathisia, myokymia, stuttering, and tics.[32,34–37] One SCA27 patient with PNKD differed clinically from patients with myofibrillogenesis regulator 1 gene mutations that frequently cause familial forms of this condition, by the development of mild mental retardation and lack of familial history.[36,38] One patient with SCA3 was described presenting with akathisia as the main neurological manifestation, which partially improved with clonazepan.[37] A few patients with postural truncal dystonia, orofacial dyskinesia, and head tremor in SCA2 and gait apraxia in SCA10 were also reported.[35]

The main strengths of this systematic review were that the search was not restricted to a single database or English-language publications, a large population of varied origin from multiple different publications was ascertained, and data extraction was limited to genetically confirmed ADCA patients. The study limitations include that statistical analysis may have been underpowered for rare SCA subtypes with few reported patients. Also, that conclusions on dopaminergic imaging or DRT response in patients with parkinsonism or dystonia, or BoT response in patients with dystonia, might be subject to reporting bias, because DRT use was reported in half of the patients with parkinsonism and only rarely was DRT or BoT treatment described in patients with dystonia.

In conclusion, movement disorders are frequently present in ADCAs. Sometimes, they can be the initial symptom, present even before development of ataxia, or sometimes even in the absence of ataxia for as long as for 30 years of disease duration. The most prominent is parkinsonism. In those cases, complementary studies are mandatory to rule out cerebellar atrophy. Alteration of the nigrostriatal pathway reported in some

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cases, as well as the response to DRT and development of motor fluctuations, are all findings requiring further clarification.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

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