Development of parkinsonism after long-standing cervical dystonia – a cohort

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Key words: dystonia, parkinsonism

Word count: 2315/3700

Abstract

Introduction: Dystonia occurring in the context of parkinsonism is well-known, e.g. as foot dystonia in young-onset Parkinson's disease (PD), anterocollis in multisystem atrophy (MSA) or blepharospasm (levator inhibition) in progressive supranuclear palsy. We have, however, encountered a series of patients whose phenotype differed from the above described entities.

Methods: We describe a cohort of patients in whom typical idiopathic isolated (primary) late-onset focal or segmental (predominantly cervical) dystonia preceded the development of parkinsonism by several years, sometimes decades.

Results: In a cohort of 450 patients followed in our botulinum toxin injections clinic, we identified 11 (2.4%; 7 women) who developed parkinsonism at a median of 14 years after the onset of dystonia. Median age at onset of parkinsonism was 70 years (range 59-87), usually manifesting with a new tremor or a change of tremor pattern, complaints of 'slowing down' or new walking difficulties. Parkinsonism resembled PD in 5 (one pathologically confirmed); the remainder had atypical parkinsonism of MSA (n=3) or indeterminate phenotype (n=3).

Conclusion: The relatively frequent occurrence of parkinsonism after long-standing dystonia would suggest a link between the two, in line with evidence from other clinical reports, imaging studies, animal models and genetics. It appears that in some cases of dystonia this could be an antecedent manifestation of a syndrome with parkinsonism developing later, or be a risk factor for parkinsonism. In practice, it is important for clinicians to be alert to new symptoms/signs in patients with long-standing dystonia. From a research point of view, longitudinal case-control studies would be required to further investigate the link between long-standing dystonia and subsequent parkinsonism.

Introduction

The links between the two archetypical basal ganglia disorders, dystonia and parkinsonism, are manifold. Dystonia occurring in the context of parkinsonism is well-known.[1, 2] For example, patients with young-onset Parkinson's disease (PD), particularly if due to PARKIN mutations, may present with foot dystonia as their first symptom[3-5]. Similarly, limb dystonia and parkinsonism in the absence of other features would prompt consideration of dopa-responsive dystonia, typically due to GCH1 mutations. A dystonic hand, and less frequently, foot posturing is a hallmark feature of corticobasal syndrome (CBS). Anterocollis in a patient with parkinsonism alerts to multiple system atrophy (MSA), and patients with progressive supranuclear palsy (PSP) often have levator inhibition, a type of blepharospasm. All these forms of dystonia typically accompany, or rarely precede by a few years only, the development of the parkinsonian syndrome. In recent years, we have however encountered a series of patients in whom typical isolated, idiopathic focal or segmental (predominantly cervical) dystonia preceded the development of parkinsonism by a long duration of several years. This observation has been possible because the long follow up of a large cohort of patients with cervical dystonia in a captive botulinum toxin clinic with quarterly follow up. These cases raise the question of a syndromic association. Pathological diagnosis was available in one case and the others are clinically characterised.

Methods

Consecutive patients with isolated focal or segmental dystonia who attended the botulinum toxin clinic between 2015-2019 at the National Hospital for Neurology and Neurosurgery, London, UK, and who had developed parkinsonism were included, and their medical records were reviewed. Written informed consent was obtained from all participants collection and the study was approved by our research ethics committee.

Results

Description of the cohort

In our cohort of 450 patients with focal or segmental dystonia all of whom attended the botulinum toxin clinic and were actively being followed up every 3 months, we identified 11 patients (2,4%) who developed parkinsonism at a median of 14 years (range 6-57 years) after the onset of dystonia. None of these patients received dopamine receptor blocking or dopamine depleting drugs. Epidemiological and clinical details as well as diagnostic test results are summarised in *table 1*, while *table 2* provides details of three representative clinical vignettes. Most patients were women (n=7) and the median age at last follow up was 79 years (range 67-90).

Clinical spectrum

Dystonia

The median age at onset of dystonia was 56 years (range 18-73). Dystonia affected the cervical region in most patients (n=10), while one patient had blepharospasm only. Five of the 10 patients with cervical dystonia had additional involvement of the arms or voice. In four patients, dystonic tremor

(either tremulous cervical dystonia or dystonic hand tremor) was a prominent feature. In case #6, dystonia phenomenology changed from torticollis and retrocollis to marked anterocollis as the patient developed parkinsonism. Another patient (case #1) reported initial worsening of cervical dystonia with L-dopa therapy; later in the disease course, the cervical dystonia spontaneously improved. In the rest of the patients, there was no noticeable change in the dystonia pattern and they continued to respond well to botulinum toxin injections.

Parkinsonism

Parkinsonism manifested at age 70 (median; range 59-87), with worsening of a pre-existing tremor (n=8), the development of walking difficulties (n=3), a combination of the former (n=3) or slowness of movement (n=1).

PD-phenotype

The parkinsonian phenotype was compatible with idiopathic PD in 5 patients - all displayed asymmetric dopa-responsive parkinsonism with rest tremor and absence of any atypical features. Median age of onset was 75 years (range, 67-80).

One patient (#1; see vignette and *video*), who initially manifested with a PD-phenotype, later developed atypical features including mild nystagmus and spontaneous retropulsion on standing. Brain pathology (see *figure*) confirmed the diagnosis of PD, but also revealed additional pathologies including (paraneoplastic) cerebellar degeneration accounting for the atypical features.

Atypical parkinsonism phenotypes
In the remaining 6 patients, there were additional features not compatible with PD.

MSA-like

Three patients presented with an MSA-like phenotype (parkinsonism accompanied by cerebellar signs), though all had additional unusual features (detailed below). The median age at onset of parkinsonism in this cohort was 61 years (range, 59-64) and median duration of parkinsonism was 7 years (range, 6-8 years). All three patients had a history of REM sleep behaviour disorder and dysautonomia. Two of these three cases met diagnostic criteria for 'probable MSA'[6], but both also had features cautioning against a diagnosis of MSA, such apraxia and cortical sensory loss with parietal atrophy on MRI (#6; see *video*), or peri-oral dyskinesia prior to treatment with L-dopa (#8). The third patient did not meet diagnostic criteria for MSA, having experienced prominent hallucinations (without any triggers or drugs) and having a family history of PD. Equally, this patient was atypical for PD, but would neither fit into the PD, PD-dementia or dementia with Lewy Bodies because of some subtle cerebellar features such as square wave jerks.

Indeterminate parkinsonism

The remaining three cases did not fit into existing diagnostic categories for atypical parkinsonism. One patient (#9) had parkinsonism, cerebellar signs (nystagmus, limb

dysmetria) and stridor, but no autonomic features, therefore not fulfilling diagnostic criteria for possible MSA and her age of onset (74y) was a red flag cautioning against such a diagnosis.

Another patient (#10) developed predominantly lower body parkinsonism at age 63 with freezing of gait and postural instability; resembling PSP, but marked her autonomic dysfunction (requiring a suprapubic catheter) was an exclusion criterion for this diagnosis [7].

The last patient of this category manifested at age 87 with falls and developed an akinetic-rigid syndrome with freezing of gait, significant cognitive (frontotemporal) dysfunction involving executive dysfunction and impairment of visuoperceptual processing, and distal, stimulus-sensitive myoclonus (#11; see *video*). Even though she didn't exhibit the full-blown picture of a CBS, she would meet clinical criteria for possible corticobasal degeneration mainly because of her cognitive profile [8].

Other observations

Three patients (1 with PD-phenotype, 2 with MSA phenotype) complained about painful leg paraesthesia, yet without electrophysiological evidence of neuropathy. All of these three had autonomic involvement (urinary incontinence, orthostatic hypotension, cardiovascular autonomic failure; see table 1).

Some patients had a family history of neurological disease: head tremor in a daughter (#2), PD in a cousin (#7), deafness in a mother (#10).

Investigations

The investigations for all the patients are listed in the *table*. All patients showed reduced tracer uptake on DAT scan. Brain imaging results were heterogeneous, reported as normal (n=1), showing small vessel disease (n=7), or atrophy (n=4; generalised atrophy, n=3: amongst these, one with parietal and one with temporomesial predominance; cerebellar and pontine atrophy, n=1). Six patients were also genetically investigated (see table)-no pathogenic mutations were found. Two patients were tested for neuronal antibodies with negative results. One patient (#1) had post-mortem brain pathology revealing PD as the main diagnosis.

Discussion

We present here a cohort who initially presented with fairly typical and isolated cranial, cervical or craniocervical dystonia. They were regularly followed up for botulinum toxin injections without developing any new clinical features for several years, and then developed new onset of parkinsonism. All had confirmatory abnormal DAT SPECT scans. Although dystonia as feature of various parkinsonian disorders is recognised[9], the patients reported here differ, as the dystonia preceded the development

of parkinsonism by a number of years and does not fit the previously reported, typical patterns (e.g. foot dystonia in young onset PD).

Broadly, these patients can be divided into two groups, namely those who developed a clinical picture consistent with idiopathic PD[10], and those who display atypical parkinsonism.

PD was the clinical diagnosis in five patients. Brain pathology in one such patient showed that he had mixed pathology and that beside his main diagnosis of PD, he also had Alzheimer pathology, amyloid angiopathy, small vessel disease and paraneoplastic cerebellar degeneration, which explains why he developed atypical features for PD later during his illness.

Three patients could be broadly classified under a "MSA-like phenotype", with two fulfilling criteria for possible MSA[6], albeit with some unusual features. Three further patients, having freezing of gait as their primary manifestation, did not fit established diagnostic criteria for either PD or atypical parkinsonism.

Of note, the patients presented here did not have any features at onset to suggest a combined or complicated dystonia syndrome, but were routinely followed in our regular botulinum toxin injections clinic and stem therefore from a cohort of adult-onset, isolated focal dystonia. In particular, they therefore do not represent complicated referrals to a tertiary referral centre. However, we are in the privileged position to be able to follow our patients for long periods and to therefore take note of any new, atypical features.

How can one explain the development parkinsonism after long-standing cervical or craniocervical dystonia?

Though some patients had small vessel disease, the abnormal DAT scan as well as the clinical picture (asymmetry and prominent involvement of upper limbs, additional features like RBD or L-dopa response) renders the consideration of vascular parkinsonism highly unlikely.

However, there is evidence from clinical reports, imaging studies, animal models and genetics that supports the notion of a connection between long-standing dystonia and the subsequent development of parkinsonism.

In 1986, two groups made observations similar to ours: Katchen and Duvoisin reported three patients who initially presented with dystonia, and developed parkinsonism up to 15 years later[11]. Interestingly, these patients share some similarities with our case #1 with regard to the observed worsening of the dystonia with L-dopa treatment, and disappearance of dystonia during the disease course[11]. Klawans and Paleologos reported eight patients with craniocervical dystonia who subsequently developed partially L-dopa responsive parkinsonism, but also with exacerbation of the pre-existing dystonia[12]. More recently, Papapetropoulos and Singer reported a case of cervical dystonia preceding PD by 12 years[13].

Our study adds to the existing literature of such case reports/series, a follow-up study of a captive cohort of predominantly cervical dystonia patients, and gives a notion of the frequency of such a conversion.

Furthermore, a prospective case-control study indicated a higher risk of developing Parkinson's disease in patients with blepharospasm (with or without more widespread involvement with

craniocervical dystonia) than controls. In this cohort, blepharospasm preceded PD by 5.6 ± 5.2 years (range 0.5-20years). [14]

Dystonia preceding parkinsonism is also seen in animal models. For example, in the paradigmatic animal model of parkinsonism, i.e. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) - induced parkinsonism, dystonia precedes the development of actual parkinsonism[15, 16]. During the acute dystonia provoked by MPTP, the monkeys displayed a decrease of striatal dopamine and dopamine 2 like receptors[15, 16]. Subclinical loss of dopamine after striatal dopamine depletion is also one important predisposing factor in an animal model of blepharospasm, together with enhanced brainstem excitability caused by an irritative corneal trauma as the second hit.[17]

Several imaging studies have also substantiated subclinical involvement of dopaminergic pathways in humans with various forms of isolated dystonia (reviewed in[18]).

Further evidence linking dystonia and parkinsonism comes from the field of genetics, where we recognise a number of genes associated with dystonia-parkinsonism. For example, PARKIN mutations carriers might present with limb dystonia decades before developing signs of parkinsonism[4]. GCH1 mutations, originally known to cause doparesponsive dystonia or Segawa's disease, are now recognised to be a risk factor for PD[19].

Lastly, dopamine receptor blocking agents (e.g. neuroleptics) are further, pharmacological proof of a link between the dopaminergic system and dystonia[20].

Having reviewed these arguments in favour of a connection between the long-standing dystonia and the subsequent parkinsonism in our patients, the possibility of long-standing craniocervcial dystonia being part and parcel of the parkinsonian syndrome (syndromic association hypothesis) comes to mind.

It may be that, as in the double-hit animal model of blepharospasm,[17] also here two factors are at play: the first hit being dopaminergic dysfunction leading to dystonia, the second hit (further?) dopaminergic cell loss (e.g. age-related) resulting in parkinsonism.

Of course, subclinical parkinsonism or a preclinical dopaminergic deficit at the time of presentation with dystonia are difficult to exclude, as isolated dystonia is not assessed using DAT scans.

If that is indeed the explanation for the present series, the ensuing clinical implication would be to recognise long-standing dystonia as prodromal feature of late-onset parkinsonism, both classic PD and atypical parkinsonism variants. This concept might find its analogy to RBD. RBD may be idiopathic, although in the majority of cases with a long enough follow up, it is prodromal to PD or other synucleinopathies like MSA or dementia with Lewy bodies.

 Similarly, it could be construed that craniocervical dystonia is typically idiopathic, but in some cases, it may herald a form of parkinsonism. Intriguingly, a high prevalence of olfactory dysfunction in patients with cervical dystonia has been reported recently.[21]

It is also known that there are higher rates of anxiety and depression in dystonia and all these non-motor features of course have resonance with parkinsonian conditions often preceding the motor manifestation by decades.

Considering the family history of neurological disease in some cases, it may be that some of the observed phenotypes are caused by genetic variants that either were not found in our testing or may

be unknown as yet. Overall, it is possible that the syndrome of long-standing dystonia with subsequent development of parkinsonism is heterogeneic.

There is the possibility that dystonia preceding PD has been underrecognised so far. Firstly, dystonia itself is underdiagnosed according to a population based study[22]. Secondly, an interesting observation in this context is the high incidence of tremor in pre-symptomatic PD, even 10 years prior to the diagnosis of PD[23]. There is epidemiological data suggesting that patients with essential tremor (ET) have a higher risk for PD[24], and there is data showing that a significant proportion of patients labelled as ET had a dystonic tremor[25, 26]. Patient #4 is an illustrative example for this hypothesis – he manifested in his youth with bilateral hand and head tremor, and would have been classified as ET. Only later did cervical dystonia become a prominent feature.

In summary, although we firstly describe the possible link between cranial/cervical dystonia and parkinsonism in a larger cohort of patients, it is in keeping with various lines of evidence supportive of this notion. The implications of our observation are twofold: For clinical practice, it is important to be alert to new symptoms in patients with long-standing dystonia. Often, these patients are seen during short appointments for treatment with botulinum toxin injections, and more subtle signs might escape attention. Red flags in our patients were the development of a new tremor or a change of the tremor pattern, complaints of slowing down or new walking difficulties. From a research point of view, longitudinal case-control studies would be required to further investigate the possible link between isolated dystonia and subsequent parkinsonism.

Figure legend.

Fig. 1.1: (a) The medial surface of the left half brain shows no significant abnormality while in the midbrain there is severe pallor of the substantia nigra (arrows). (b) Hematoxylin and eosin staining (HE) showing severe loss of neurons in the substantia nigra. Lewy bodies immunoreactive for α-synuclein in the cytoplasm of dopaminergic neuron in the substantia nigra (arrowheads) (c). Frequent diffuse and moderate mature amyloid β (Aβ) deposits in the parietal lobe (d). Phosphorylated tau (AT8)-positive neurofibrillary tangles and threads extending to the temporal cortex (e). Capillary cerebral amyloid angiopathy immunopositive for Aβ in the occipital lobe (f). AT8-positive thorny astrocytes in the sub-pial region of the temporal lobe (g). Immunohistochemical staining for α-synuclein (c), Aβ (d, f) and AT8 (e, g). Bars = 20 μm.

Fig. 1.2: The coronal slice at the level of the accumbens showing a dark nodule in the frontal white matter (a) and pleomorphic neoplastic cells containing melanin (b). Severe loss of Purkinje cells with proliferation of Bergman's glia and loss of granule cells in the cerebellum. HE (b, c). Bars = 100 μm

Video legends.

Video 1: The video shows patient #1 at the age of 86, still with torticollis but also displaying a staring expression, bradykinesia and hypophonic speech; postural instability (not shown) has rendered him wheelchair-bound.

Video 2: The video shows patient #6, the first segment at age 58, when she just had developed the first parkinsonian symptoms. She has a torticollis to the left, and a reduced arm swing on the left with mild bradykinesia. The second segment shows her 9 years later. She is wheelchair bound and has a severe anterocollis, and experiences dizziness when standing up. She walks with a short-stepped, shuffling gait with some start hesitation and freezing. There is generalised bradykinesia left

more than right. She has difficulty copying meaningless gestures. Eye movement examination shows broken pursuit and endgaze nystagmus.

Video 3: The video shows patient #11 at the age of 87. There is still cervical dystonia, but she also has an unsteady gait with impaired postural reflexes, with reduced left arm swing and a tendency to lean on the left. She has great difficulties copying meaningless gestures, some irregular myoclonic jerks, and bradykinesia on the left more than the right.

Statement concerning ethics and informed written consent:

We hereby confirm that the present study conforms to the ethical standards and guidelines of the journal. The patients have given written and informed consent for online publication of their videos.

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