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Review article

Remission in dystonia – Systematic review of the literature and meta-analysis

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ABSTRACT

In isolated, sporadic dystonia, it has been occasionally reported that some patients might undergo symptom remission. However, the exact clinical characteristics of patients with remission remain understudied. Given the important prognostic and pathophysiological implications of dystonic remission, we here provide a systematic review of the literature and a meta-analysis to assess demographic and clinical features associated with this phenomenon. We also provide a list of operational criteria to better define dystonic remission. Using PubMed and Embase, we conducted a systematic literature search in March 2018. 626 records were screened, 31 studies comprising data of 2551 cases with reports predominantly from patients with cervical dystonia (n = 1319) or blepharospasm/Meige syndrome (n = 704) were included in qualitative analysis. Five studies reporting remission in cervical dystonia were eligible for meta-analysis. Complete remission was reported in 11.8% and partial remission for 4.4% of cases. Remission rates were higher in cervical dystonia than in blepharospasm/Meige (e.g. complete remission 15.4% vs. 5.8% respectively). Remission occurred on average 4.5 years after onset of dystonic symptoms. However, the majority of patients (63.8%) relapsed. Meta-analysis for cervical dystonia showed that patients with remission were significantly younger at symptom onset than patients without remission (mean difference −7.13 years [95% CI: 10.58, −3.68], $p < 0.0001$). Based on our findings, we propose that the *degree*, the conditions associated with the *onset*, and the *duration* of remission are key factors to be considered in a unifying definition of dystonic remission.

1. Introduction

Dystonia is a movement disorder characterized by abnormal movements and/or postures due to involuntary muscle contractions [1]. Dystonia has a wide range of etiologies and often co-occurs with additional clinical signs (combined or complex dystonia) in the context of neurodegenerative disorders [2] or as a result of brain lesions [3,4]. Isolated dystonia refers to cases where beyond the presence of dystonia (with or without concomitant tremor) there is nothing else [1]. In familial cases of isolated dystonia, several genes have now been identified [5] and genotypic-phenotypic correlations have provided important information on long-term prognosis. However, in sporadic isolated dystonia – in the old literature also referred to as "primary" dystonia – relatively little progress has been made. These cases are classified based on the distribution of dystonic symptoms at onset, but very little is known with regard to prognosis, as for example their severity progression or somatotopic spread [6–8]. It has been occasionally reported that some patients with isolated sporadic dystonia might experience symptom remission, but this has not been systematically assessed. In an era where treatment options expand beyond oral medication or botulinum toxin injections and also entail surgical interventions, the possibility of sustained remission has very important implications. Knowing which patients might undergo sustained remission could, therefore, be crucial for patient counseling and appropriate treatment selection. Hence, to provide a clear overview of the existing reports on dystonic remission, we here conducted a systematic review of the literature. We also aimed to perform a meta-analytic study, in order to specifically address whether some demographic and clinical features are more prevalent or are associated with dystonic remission.

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2. Methods

In March 2018, we conducted a systematic literature search in PubMed (http://www.ncbi.nlm.nih.gov) and Embase (https://www.elsevier.com/solutions/embase-biomedical-research) using the keywords “dystonia”, “dystonic”, “cervical dystonia”, “torticollis”, “blepharospasm”, “Meige”, “cranial dystonia” and “writer's cramp” in combination with the keywords “remission/s”, “recovery” and “cure”, respectively. Additionally, the bibliographies of relevant articles were scanned for further suitable literature. We considered only articles containing data of original clinical studies in English and German language. Duplicate articles, reviews, and opinions/comments were excluded. We screened the abstracts and full texts, if available, for relevant information, which was then systematically entered into a comprehensive table. We excluded case reports to avoid overestimation of remission. Articles referring to combined dystonic syndromes (e.g., myoclonus-dystonia) and acquired causes of dystonia (e.g., due to brain lesions), as well as studies where surgical interventions, as for example myotomy or deep brain stimulation, were performed, were also not considered. Cases of improvement due to medication, characteristically in dopamine-responsive dystonia, or due to direct effects of botulinum toxin (i.e. improvement with ongoing botulinum toxin injection treatment) were also excluded. Additionally, we excluded reports of fixed dystonia that might be associated with a different underlying etiology and tardive dystonic syndromes (see Fig. 1). The review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [9].

We classified remission as complete in cases in which a full resolution of dystonic symptoms was reported regardless of its duration or a subsequent recurrence of dystonic symptoms. Partial remission was considered in all other cases in which improvement, but not complete resolution of symptoms was stated (e.g., “substantial recovery”, “much/moderate/slight improvement”). Whenever both objective (clinical neurological evaluation or validated scales) and subjective measures (e.g. patient reports) of remission were available, we only relied on the former.

Further, studies were selected for meta-analysis, if they involved a comparison between patients with and without remission (e.g. gender specification, age at onset of the disease, disease duration) and exact numbers of patients could be categorized, and where means and standard deviations were given or could be calculated from the reported data. Eventually, 5 studies reporting remission in patients with cervical dystonia (CD) fulfilled these criteria, the data of which were pooled into a random-effects model with regard of age at onset and disease duration, in line with the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) [10]. We additionally undertook consideration of all the included studies in the pooled analysis to estimate clinical heterogeneity. This was done employing, primarily, the I^2 statistic, which provides an estimate of the percentage of inconsistency thought to be due to chance, alongside the Chi^2-p value that provides

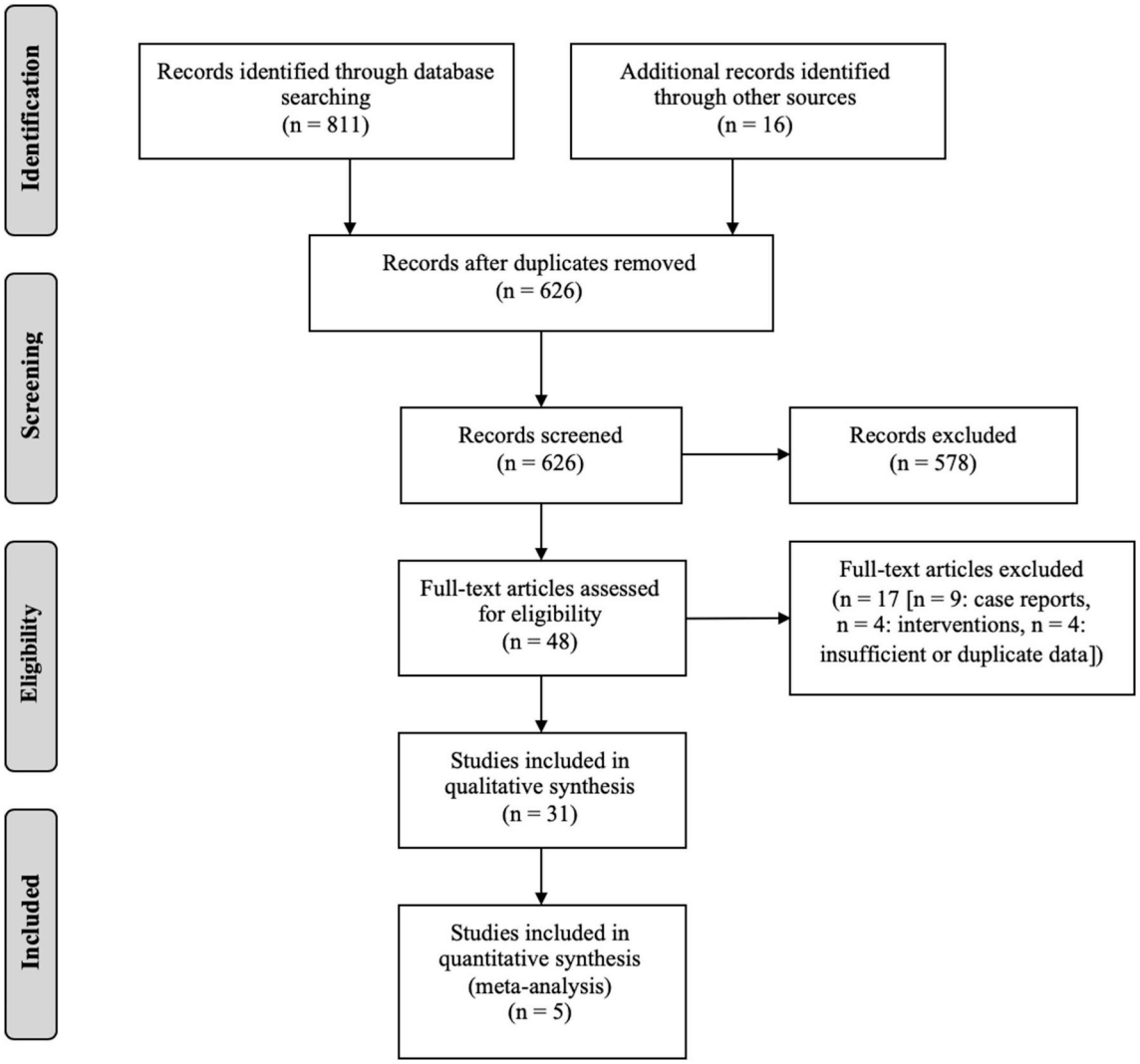

Fig. 1. Flow diagram of the systematic review (according to Ref. [9]).

Table 1
Demographic data of the patient cohort.

	No. of patients, n (%)	Female gender, %	Age at onset of dystonia, years (range)	Disease duration, years (range)
Total	2551	60%	42 (1–82)	7.3 (0–54)
Cervical dystonia	1319 (51.7%)	59.7%	39.4 (3–76)	5.7 (0–54)
Blepharospasm and Meige-Syndrome[a]	704 (27.6%)	67.1%	56.2 (19–82)[c]	n/a
Generalized dystonia	21 (0.8%)	n/a	n/a (1–31)	n/a
Embouchure dystonia	26 (1%)	n/a	37.9 (n/a)	n/a
Others[b]	481 (18.9%)	63.3%	48.1 (2–81)	11.1 (n/a)

In categories, where no data was available for the different dystonic subgroups, the total was calculated based on the remaining available data.
n/a = not available.
[a] Phenotypic distinction between blepharospasm and Meige-syndrome was not possible for most studies.
[b] Insufficient data to identify exact clinical phenotype.
[c] Data available for < 100 patients.

the strength of evidence for heterogeneity [11]. The latter analyses were performed with RevMan, version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. These results are indicated as standardized mean difference (SMD) with 95% confidence intervals (CIs). Categorical data was compared using chi-square-tests. Level of significance was set at $p < 0.05$.

3. Results

In total, 626 articles were identified (see supplement 1). After the screening process, 31 articles comprising data of 2551 patients were included in the final analyses. The majority of reported cases referred to cervical dystonia (CD; n = 1319, 51.7%), followed by either blepharospasm (BSP) or Meige syndrome (n = 704, 27.6%). Phenotypic classification of 481 (18.9%) patients was not possible, due to insufficient clinical data. A complete list of reported phenotypes and their frequencies is provided in Table 1.

A clear definition of remission was provided in only 8 of 31 studies (25.8%) (see supplement 2). Among these, 4 studies required a minimum duration of symptom improvement of 1 year to allocate patients in the remission group [12–15]. In the majority of studies (n = 27/31) remission was evaluated by physicians.

Overall, complete remission (CR) was reported for 301 (11.8%) and partial remission (PR) for 113 (4.4%) of identified cases. In patients with CD, remission rates were approximately threefold higher than in patients with BSP and Meige syndrome (CD: CR 15.4%, PR 7.4% vs. BSP/Meige syndrome: CR 5.8%, no PR). In generalized dystonia remission rate was 23.8%, however, we could only collect data from a single case series [16]. No remissions were reported in patients with embouchure dystonia (see Table 2). The mean age of disease onset in patients with remission was lower than the age of onset in the whole group (34.7 vs. 42 years). On average, remission was reported to occur 4.5 years (3 months–22 years) after the onset of the disease.

Dystonic relapse was reported in eleven studies. In total, data from 163 patients undergoing remission was available. Of those, relapse was reported in 63.8% (n = 104) and ranged from 58.7% in CD to 100% in generalized dystonia [13,15–24]. Remission duration (either to relapse or last follow-up) was shorter in patients with CD (2.7 years) than in patients with BSP and Meige syndrome (7.1 years) (available data reported in Table 2).

Meta-analysis showed that the age of onset in patients with CD and remission was significantly lower than in patients without remission (mean difference −7.13 years [95% CI: 10.58, −3.68], $p < 0.0001$; Fig. 2a). There was no significant heterogeneity among the included studies [$I^2 = 8\%$, $p = 0.36$]. There was no significant difference in disease duration between patients with CD and remission and those without remission (mean difference 2.75 years [95% CI: 0.48, 5.97], $p = 0.09$; Fig. 2b). Gender distribution also did not differ between the two groups (remission: 38 males, 63 females, non-remission: 171 males, 267 females, $\chi^2 = 0.0694$, $p = 0.792$).

4. Discussion

In our reviewed sample of 2551 patients with dystonia, remission was reported in 16.2% of cases. Among the focal dystonias, rate of reported remissions was higher in CD (22.8%), than in BSP or Meige syndrome (5.8%). There were no systematic reports of remission in task specific dystonias, such as focal hand dystonia and in fact, a single study, which assessed remissions in embouchure dystonia found no such cases [25]. There were also no reports of remission in monogenic isolated dystonias. Although one study did report high remission rates for generalized dystonia (23.8%), all 5 remission cases relapsed, and several medications had been tried throughout the course of dystonia [16].

To some extent, the high prevalence of remission rates in CD reflects the overall prevalence of CD, as it is the most common form of focal dystonia [26–28]. However, prevalence alone cannot account for the threefold increase of remission rate in CD compared to BSP/Meige syndrome, which is the next most commonly reported phenotype [26–28]. Therefore, additional factors contribute to the increased likelihood of remission in CD compared to other isolated dystonias. Indeed, based on our meta-analysis, CD patients with remission were younger at symptom onset than patients without remission (average of 7.1 years). Although the exact effect of age as a phenotypic modifier of CD remains underexplored, previous data suggested that age at onset of CD is associated with different expression of dystonic symptoms [29]. Patients who were younger at the manifestation of CD had more focal presentations compared to patients with older age at onset, where widespread dystonic symptoms (i.e. segmental dystonia) prevailed [29]. On one account, the somatotopic extent of dystonic symptoms also serves as a behavioral marker of the magnitude of neuronal deficits leading to dystonia [30–35]. Accordingly, the more restricted forms of CD would also be associated with more confined neuronal deficits and, thereby, increased likelihood of compensatory changes [36,37] to occur that could lead to symptom remission. In contrast, patients with more widespread patterns of dystonic symptoms, as those with older age at onset and segmental dystonia [29], would have a lesser probability of neural compensation and, thereby, remission. A key prediction of this approach is that the overall likelihood of remission for the different dystonic phenotypes depends on the magnitude of the underlying neural deficits. Indeed, our results do seem to support the simple analogy between the number of neurons involved in the cortico-subcortical sensorimotor representations for the different body areas (e.g. neck versus face) and the probability of remission for the different dystonic phenotypes (CD > BSP/Meige).

The suggestion that remission is influenced by the extent of the dystonic deficit is also corroborated by the finding that the time period, during which remission occurred, was on average within the first 5 years of the disorder. Importantly, this was true for both CD (mean 4.5 years) and BSP/Meige syndrome (mean 4.4 years) (no data available for generalized dystonia; see Table 2). Indeed, this initial period after

Table 2
Descriptive data of patients with remission in dystonia.

	Complete remission, n (%)	Partial remission, n (%)	Observation of outcome by physician, no. of studies (%)[a]	Age at onset, years (range)	Gender female, %	Disease duration, years (range)	Follow-up period, years (range)	Disease onset to remission, years (range)[b]	Duration of remission, years (range)[c]	Relapse[d], n (%)
Total	301 (11.8%)	113 (4.4%)	27 (87.1%)	34.7 (9–69)	62.4%	6.8 (4mo–31y)[e]	7.5 (9mo–33y)	4.5 (3mo–22y)	3.9 (1mo–40y)	104 (63.8%)
Cervical dystonia	203 (15.4%)	97 (7.4%)	18 (90%)	34.7 (9–69)	61%	8.1 (4mo–31y)[e]	6 (9mo–33y)	4.5 (6mo–17y)[e]	2.7 (1mo–29y)[e]	74 (58.7%)
Blepharospasm and Meige-Syndrome	41 (5.8%)	–	4 (66.7%)	n/a	67.9%[e]	4.4 (1–22)[e]	10.2 (1.9–11)	4.4 (3mo–22y)[e]	7.1 (1–17.5)[e]	–
Generalized dystonia	5 (23.8%)	–	1 (100%)	n/a	n/a	n/a	16 (n/a)[e]	n/a	n/a	5 (100%)
Embouchure dystonia	–	–	1 (100%)	–	–	–	6 (n/a)[e]	–	–	–
Others	52 (10.8%)	16 (3.3%)	3 (100%)	n/a	n/a	3.5 (n/a)[e]	1.17 (n/a)[e]	3.5 (n/a)[e]	n/a (1mo–40y)[e]	25 (83.3%)[e]

In categories, where no data was available for the different dystonic subgroups, the total was calculated based on the remaining available data.
n/a = not available.
[a] Insufficient data from n = 2 studies.
[b] Including data from patients with sustained remission.
[c] Time period was calculated until last follow up or reported relapse.
[d] Relapse was explicitly assessed in n = 11 studies.
[e] Data available for < 100 patients.

symptom onset is critical, as it provides the time frame during which dystonia spreads to contiguous body parts, particularly in BSP [7,38]. According to our hypothesis here, patients at incipient risk of dystonic spread would have a lesser probability to undergo remission.

On a different, possibly complementary account, the likelihood of dystonic remission might also depend on the probability of occurrence of the motor programs that are also involved in the expression of dystonic symptoms. Indeed, in task-specific dystonias, including hand and embouchure dystonia it might be impossible to avoid using motor programs that also specifically cause dystonia [39]. In contrast, in CD and BSP/Meige syndrome, motor program specificity might not be associated with the manifestation of dystonia and hence chances of symptom compensation and, thereby, remission (also see below) might be greater. The lack of unequivocal reports on remission in other focal dystonias, as for example task-specific dystonias (e.g. focal hand/musicians' and embouchure dystonia) means that we cannot further explore these different hypotheses.

Changes in somatosensory processing of stimuli and sensorimotor integration are key findings in focal dystonia, including CD [40–43]. Crucially, processing and integration of somatosensory stimuli are age-dependent functions that decline in elder populations [44–46]. One might, therefore, argue, that with increasing age, the capacity to provide accurate computations of somatosensory input and sensorimotor integration is reduced. This, in turn, could also decrease the probability of symptom compensation associated with clinical remission in dystonia, as for example CD. This pathophysiological approach also highlights the role of sensory tricks, which are particularly prevalent in CD [47]. Evidently, sensory tricks lead to a temporary improvement of dystonic symptoms and could be, therefore, viewed as a reflection of the capacity to gain behavioral control over pathological motor output [47]. Somewhat counterintuitively, therefore, one paper suggested that absent sensory tricks in CD patients would be associated with increased likelihood of remission [19]. However, the exact phenomenology of CD (focal or segmental) was not well defined in this study and subsequent reports did not further replicate this finding [15,17]. In the absence of systematic data regarding sensory tricks in patients with and without remission no strong conclusions can be drawn.

Although data was only available from a subset of reported remission cases (163/414), the majority of patients relapsed (64%). This is unsurprising, as progression of dystonic pathology, particularly within the first years and, as aforementioned, increasing age would be associated with a failure of compensatory mechanisms to prevent the expression of abnormal movements. This would in turn lead to clinical worsening or even re-emergence of dystonic symptoms. The fact that relapse typically occurred within a few years after the onset of remission further highlights the fragile equilibrium between the factors associated with symptom compensation and a progression of dystonic pathology. Although relapse occurrence appeared to be less common in CD (58.7%) than in generalized dystonia (100% relapse rate), we do note that this might be due to an underestimation bias. Indeed, relapse was not systematically addressed in the majority of studies and the average follow-up period was relatively brief in CD, as compared to other dystonic phenotypes, for example BSP/Meige syndrome.

The lack of systematic studies in the clinical phenomenon of dystonic remission highlights several, still unresolved questions. First of all, the very definition of remission in the context of dystonia remains unclear. In the medical literature, the term remission (from the latin *remittere, "to send back")* refers to a state of absence of disease activity in a formerly affected patient [48,49]. Accordingly, we here used the terms of *complete* and *partial* remission to indicate either absence or improvement of dystonic symptoms and signs, respectively. However, among the studies we reviewed, only a quarter provided definitions of remission, whereby in most cases these definitions differed (see supplement 2). This heterogeneity also reflects the overall lack of consensus of remission in neurological disorders [50–52], including movement disorders [53]. Based on our extensive review and our critical analysis of the data we suggest the following remission criteria for dystonia. First, we define the *degree of remission* as complete, in the absence of any dystonic symptoms as documented both by objective clinical measures (e.g. clinical observation, scale-based evaluation) and by subjective patient report. We recommend the term of partial remission to be given to cases with incomplete resolution of symptoms according to clinical evaluation alone. Indeed, patient judgments might differ from clinical observation [54], particularly with regard to dystonic severity and might be influenced from other factors, as for example presence of pain or neuropsychiatric comorbidities as depression [55]. It is, therefore, crucial that partial remission relies on clinical evaluation alone. In addition, and given the common fluctuation of dystonic symptoms, we recommend the strict arbitrary criterion of a minimum 50% improvement, as assessed through a phenotype-specific

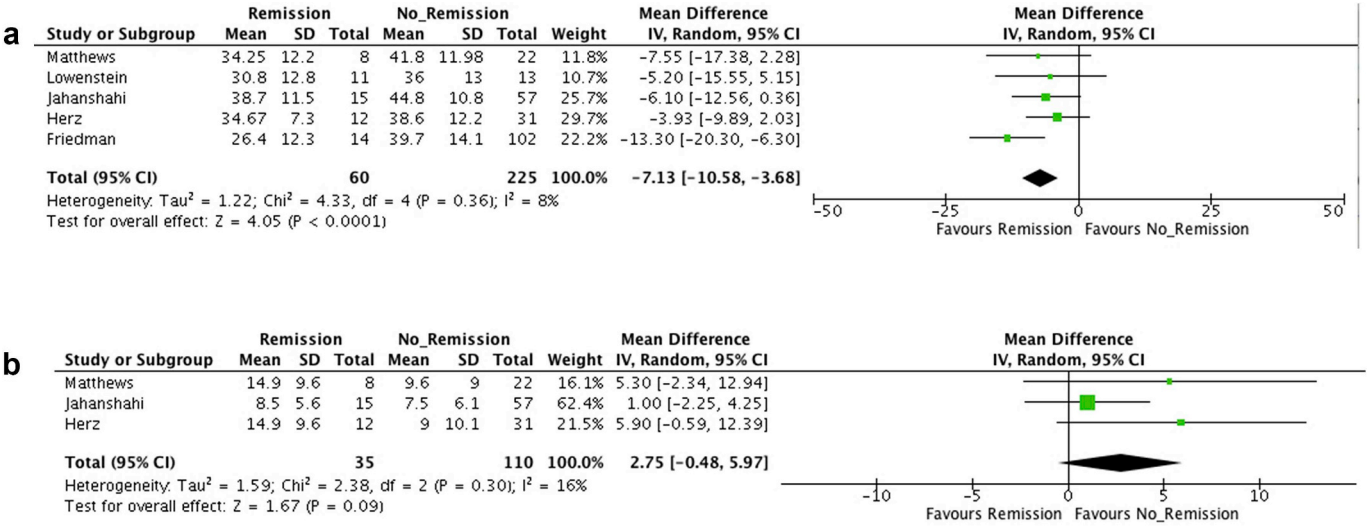

Fig. 2. Forest plot of the effect sizes from the studies comparing patients with and without remission in cervical dystonia. Horizontal lines represent 95% confidence intervals. The area of squares is proportional to the studies' sample size. A: Age at disease onset, B: disease duration.

clinician-based dystonic scale in order to document partial remission. Second, we suggest a distinction with regard to the *onset of remission*. We recommend the usage of the term *spontaneous remission* for cases, where resolution or improvement of dystonic symptoms occurs in the absence of previous pharmacological or surgical (e.g. deep brain stimulation) treatments. All other cases, where remission occurred following a treatment intervention, would fall within the *post-treatment* remission group. Indeed, the suggestion that the application of certain treatments in dystonia might potentially lead to long-term benefits due to specific disease-modifying properties has been advanced before [12,56]. Crucially, for patients of the *post-treatment remission* group dystonic symptom improvement would continue to occur in the absence of ongoing treatment. Here, therefore, the introduction of *remission duration* is important. Given the extended effects of certain treatments (e.g. botulinum toxin injections might lead to long-term responses in some patients [12]), we recommend that for remissions of the *post-treatment* group, any previous intervention should have occurred at least 12 months prior to current clinical evaluation. This period is clearly long enough to allow for remaining pharmacological or other effects of medical interventions to resolve [57–59]. Conversely, for the *spontaneous remission* group, we suggest that a remission duration of at least 6 months is sufficient to document symptom improvement (also see Table 3). Clearly, these criteria do not apply to cases with functional dystonia, where clinical presentations are typically inconsistent over time.

Our approach has several limitations. First, our systematic literature review revealed 31 suitable studies comprising data for 2551 dystonia patients. However, and despite this relatively large number, we could not identify robust datasets on other forms of dystonia, as for example focal hand or monogenic forms of dystonia. Similarly, we could not collect any data on remission rates in tremulous vs. non-tremulous dystonia, particularly CD. As our results suggest phenotype-specificity, little can be, therefore, inferred for these different forms of dystonia, but future prospective studies might be able to address these issues further. Second, although we excluded case reports to avoid overestimation of dystonic remission, we cannot dismiss the likelihood of ascertainment bias in our results. Third, although we did not include studies reporting acquired forms of dystonia or patients with clinical remission under ongoing medical treatments, some papers we included provided limited clinical information in this regard. Hence, we cannot completely rule out the possibility that some of the cases we analyzed did not in fact refer to patients with acquired causes of dystonia or patients who experienced symptom improvement due to ongoing medical treatment. However, the number of these patients would be comparatively small to our overall sample, as we excluded all cases where this was clearly stated. We were also surprised that many of the studies we identified had been conducted before clear definitions of dystonia were reached [14,16,20,21,60–63], and we could not identify any study on dystonic remission following the consensus statement on dystonia of the Movement Disorders Society in 2013 [1]. Given the difficulties in distinguishing organic from functional dystonia in many cases, we believe that some of the patients reported here could have had a functional etiology. Indeed, 14 of the 31 studies we identified were published prior to Fahn and Williams' proposed criteria for functional (at the time labeled as "psychogenic") dystonia [64]. However, compared to other functional movement disorders, patients with functional cervical dystonia are relatively rare [65–67] and their classic phenomenology is typically distinctive [67,68].

To conclude, we here assessed the prevalence and clinical characteristics of remission in isolated sporadic dystonia. We show that

Table 3
List of suggested operational definition criteria for dystonic remission.

Degree of remission
• Complete Full resolution of dystonic symptoms[a] based on objective clinical documentation and subjective report
• Partial Incomplete resolution of dystonic symptoms as documented objectively by clinician. A minimum of 50% improvement assessed through phenotype-specific clinician-based severity rating scales is required.
Onset of remission
• Spontaneous Remission occurring in the absence of any previous medical treatment for dystonia
• Post-treatment Remission occurring following past medical treatment for dystonia
Duration of remission
• Minimum period of six months if onset occurred spontaneously
• Minimum period of 12 months, since last medical intervention or any medication for dystonia
• When the duration of symptom resolution is shorter, remission should be classified as "possible"

[a] i.e. postures and movement, and not solely pain and/or discomfort.

remission was most prevalent in CD (22.8%), but was also reported for BSP/Meige (5.8%) and in a few cases of generalized dystonia. For CD, patients with remission were characterized by younger age at onset compared to patients without remission and there was no influence of disease duration or gender. Remission typically occurred within the first 5 years of the disorder, but the majority of patients relapsed. In the absence of a uniform concept of remission in dystonia, we provide a list of operational definition criteria based on the *degree*, *onset* and *duration* of dystonic remission (Table 3). We hope, that our work here will advance the documentation and characterization of dystonic remission cases in the future, particularly those with CD and a younger age at onset. This may in turn provide important insights into the clinical characteristics and further prognostic factors related to this less common but important clinical phenomenon.

Conflicts of interest

The authors disclose no conflicts of interest regarding this manuscript.

Documentation of author roles

1. Research project: A, conception, B, organization, C, execution; 2. Statistical analysis: A, design, B, execution, C, review and critique; 3. Manuscript: A, writing of the first draft, B, review and critique.

TM: 1A, B, C, 2A, B, C, 3A, B.
RE: 1C, 2A, B, C, 3B
JR: 2C, 3B
AAK: 2C, 3B
KPB: 2C, 3B
CG: 1A, B, C, 2A, B, C, 3A, B.

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Appendix A. Supplementary data

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