Can We Clearly Define Appropriate Patient Populations for Trials?

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Disclosure

No relevant conflicts of interest.

The Charge

The basic diagnostic criteria for the common focal dystonias in relation to trial design.

What patients should be entered into a trial?

The focal dystonias

- Albanese et al. 2013
- Axis I: Body distribution: Focal
- “Typical examples of focal forms are blepharospasm, oromandibular dystonia, cervical dystonia, laryngeal dystonia, and writer’s cramp. Cervical dystonia, is considered a form of focal dystonia, although by convention the shoulder can be included as well as the neck.”

…but there is also
(from the outset or by spread)

- Segmental dystonia:
  - "Two or more contiguous body regions are affected. Typical examples of segmental forms are: cranial dystonia (blepharospasm with lower facial and jaw or tongue involvement) or bibrachial dystonia."
- Multifocal dystonia:
  - "Two noncontiguous or more (contiguous or not) body regions are involved." An example would be blepharospasm and writer's cramp.

- Not to be considered: generalized dystonia or hemidystonia

Risk of spread in adult-onset isolated focal dystonia: a prospective international cohort study

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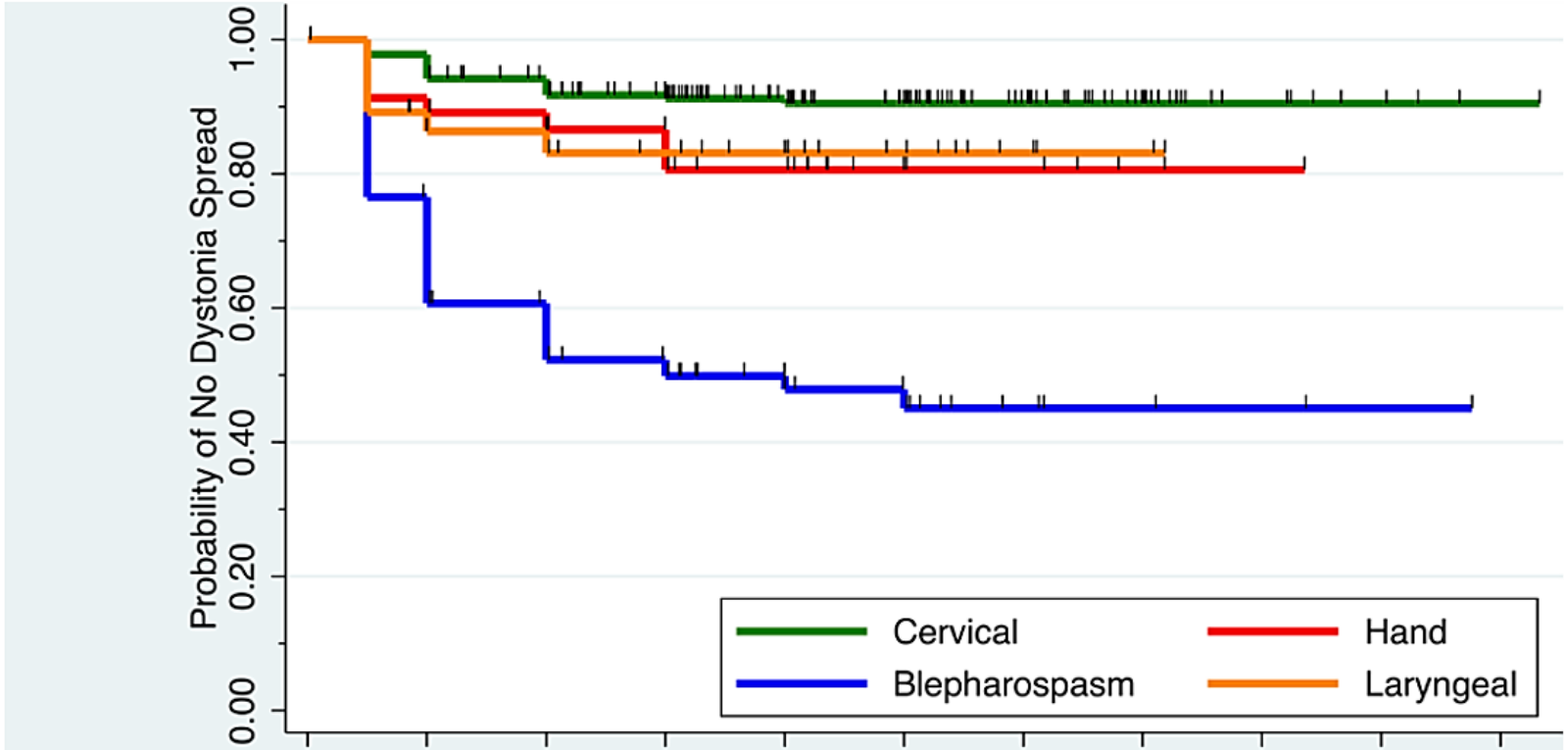

Number at risk											
Cervical	286	270	231	176	122	87	41	20	8	4	1
Blepharospasm	116	87	65	43	25	17	5	3	2	1	0
Hand	47	42	35	29	22	9	5	2	1	0	0
Laryngeal	38	31	27	20	16	9	4	2	0	0	0

How much are we willing to lump together?

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REVIEW ARTICLE

Do primary adult-onset focal dystonias share aetiological factors?

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Yes!

How much should we split?

- Cervical dystonia
  - Different directions of motion
    - Torticollis
    - Laterocollis
    - Retrocollis
    - Anterocollis
  - With and without tremor
    - Tremor of the neck
    - Tremor of the arm

Patients with predominant retrocollis, anterocollis, and neck tremor are often not included in clinical trials of botulinum toxin

How much should we split?

- Focal hand dystonia
  - Occupation
    - Writer's cramp
    - Musician's cramp
    - Many more….
  - With and without tremor
- Task specific tremor??
  - Primary writing tremor

How much should we split?

- Blepharospasm
  - Actual spasm
  - Frequent blinking

And then there is
Apraxia of
Eyelid Opening

Is increased blinking a form of blepharospasm?

No!

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ABSTRACT

Objective: The aim of this study was to investigate whether increased blink rate (BR) is part of the clinical spectrum of primary blepharospasm (BSP).

Methods: We enrolled 40 patients (16 patients with an increased BR but without typical orbicularis oculi [OO] spasms, and 24 patients with typical involuntary OO spasms) and 18 healthy subjects. The BR, blink reflex recovery cycle, and somatosensory temporal discrimination threshold (STDT) were tested in patients and controls.

Results: Patients who had typical OO spasms had an altered R2 recovery cycle whereas those who had an increased BR alone had a normal blink reflex recovery cycle. STDT values were higher in patients than in healthy subjects and no difference was found in the STDT abnormalities in the 2 groups of patients.

Conclusions: Our study shows that, despite the similar STDT abnormalities, the different changes in the R2 recovery cycle in patients with BSP and those with increased BR alone suggest that these disorders arise from different pathologic mechanisms. *Neurology*® 2013;80:2236-2241

Diagnostic Algorithms

- Cervical dystonia – no, under development
  - Note new analysis of Dystonia Coalition data by Kilic-Berkmen et al.
  - Proposes CD should include neck tremor and shoulder involvement
- Limb dystonia – no
- Laryngeal dystonia – attempt at an algorithm did not work well
  - However, there is a Delphi-based Spasmodic Dysphonia Attributes Inventory (Ludlow et al. 2018)
- Blepharospasm -- yes

Development and validation of a clinical guideline for diagnosing blepharospasm

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ABSTRACT

Objective: To design and validate a clinical diagnostic guideline for aiding physicians in confirming or refuting suspected blepharospasm.

Methods: The guideline was developed and validated in a 3-step procedure: 1) identification of clinical items related to the phenomenology of blepharospasm, 2) assessment of the relevance of each item to the diagnosis of blepharospasm, and 3) evaluation of the reliability and diagnostic sensitivity/specificity of the selected clinical items.

Results: Of 19 clinical items initially identified, 7 were admitted by content validity analysis to further assessment. Both neurologists and ophthalmologists achieved satisfactory interobserver agreement for all 7 items, including "involuntary eyelid narrowing/closure due to orbicularis oculi spasms," "bilateral spasms," "synchronous spasms," "stereotyped spasm pattern," "sensory trick," "inability to voluntarily suppress the spasms," and "blink count at rest." Each selected item yielded unsatisfactory accuracy in discriminating patients with blepharospasm from healthy subjects and patients with other eyelid disturbances. Combining the selected items, however, improved diagnostic sensitivity/specificity. The best combination, yielding 93% sensitivity and 90% specificity, was an algorithm starting with the item "stereotyped, bilateral, and synchronous orbicularis oculi spasms inducing eyelid narrowing/closure" and followed by recognition of "sensory trick" or, alternatively, "increased blinking."

Conclusion: This study provides an accurate and valid clinical guideline for diagnosing blepharospasm. Use of this guideline would make it easier for providers to recognize dystonia in clinical and research settings. *Neurology*® 2013;81:236–240

4 experts identified 19 possible signs

10 experts opined about their validity

4 features identified as possibly useful

Table 1 Content validity analysis testing the clinical phenomenology of blepharospasm

Items	Content validity ratio
1. Involuntary narrowing/closure of the eyelids due to orbicularis oculi spasms[a]	1
2. Presence of Charcot sign[b]	0
3. Increased blinking rate[a]	0.6
4. Bilateral symptoms[a]	1
5. Stereotyped pattern of spasms[a]	0.8
6. Symmetrical spasms	0
7. Synchronous spasms[a]	0.55
8. Apraxia of eyelid opening[c]	0.3
9. Hyperactivity of frontal muscles	0
10. Spasms in the lower face	0.2
11. Dystonia in other body sites	0
12. Effective sensory trick[a]	0.55
13. Presence of ocular symptoms	0.2
14. Photophobia/photo-oculodynia	0.4
15. Inability to voluntarily suppress the spasms[a]	0.8
16. Absence of premonitory sensations	0.4
17. Absence of orbicularis oculi muscle paresis	0
18. Absence of eyelid ptosis	0.2
19. Absence of double vision	0

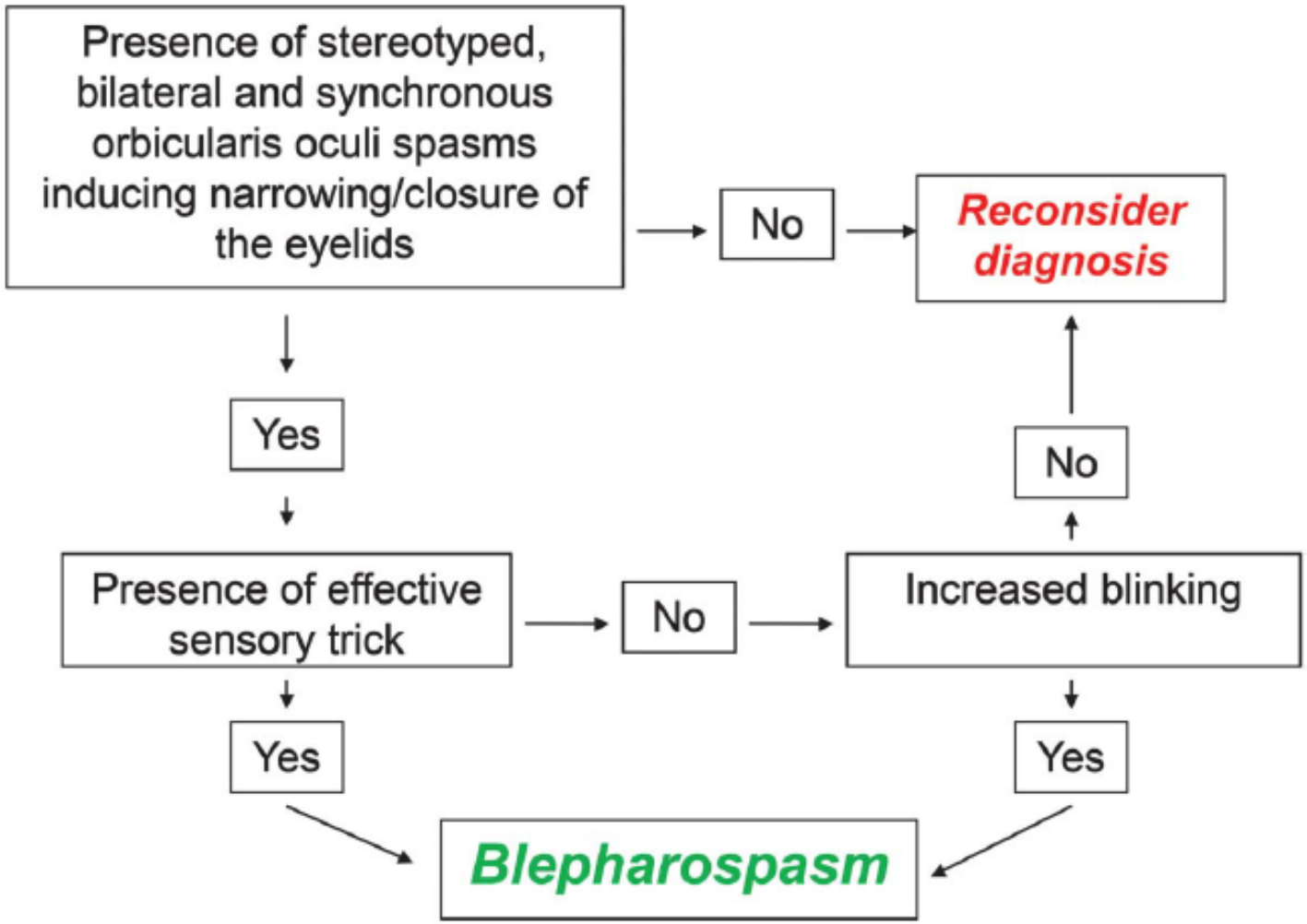
5 experts evaluated the value of the 4 features with blinded video review of 30 blepharospasm patients, 30 disease controls, and 10 normal subjects

Table 2 Sensitivity and specificity of clinical items scoring >0.5 on content validity ratio analyses in diagnosing blepharospasm[a]

	Neurologists		Ophthalmologists	
Clinical items	Sensitivity	Specificity	Sensitivity	Specificity
1. Involuntary narrowing/closure of the eyelids due to orbicularis oculi spasms (spasms must be bilateral, synchronous, and stereotyped)	100	85	95	85
2. Sensory trick	60-64	87-90	59-65	85-90
3. ≥16 blinks/min (subject at rest, eyes open)	88-90	65-70	85-88	66-70
4. Inability to voluntarily suppress the spasms (inner volitional effort rather than voluntary compensatory frontalis muscle overactivity)	32-37	70-74	30-35	68-74

[a] Data are percentages, and refer to the range of estimates obtained by 3 neurologists and 2 ophthalmologists.

Figure 2 Guideline for diagnosing blepharospasm



Sensitivity 93%
Sensitivity 90%

Validation of Diagnostic and Screening Scales for Blepharospasm

(under review)

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- 4 features were reconsidered
  - Presence of spasms
  - Sensory trick
  - Increased blinking (eye closures)
  - Inability to voluntarily suppress spasms
- 8 raters reviewed 40 videos each from a sample of 53 with blepharospasm and 53 healthy/disease controls; then reviewed 5 of the 40 videos 2 weeks later
- Intra- and inter-rater reliability were good

Sensitivity and specificity analysis

Item	Sensitivity/specificity
1. Spasms	95%/78%
2. Sensory trick	58%/94%
3. Increased eye closures	85%/50%
4. Inability to suppress	87%/52%
1 + 2	56%/98%
1 + 3	82%/84%
1 + 4	84%/84%
1 + (2 or 3) (algorithm of initial paper)	90%/82%
1 + (2 or 4)	88%/83%
1 + (2 or 3 or 4)	92%/79%

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ORIGINAL ARTICLE

Expert recommendations for diagnosing cervical, oromandibular, and limb dystonia

Giovanni Defazio[1] · Alberto Albanese[2] · Roberta Pellicciari[3] · Cesa L. Scaglione[4] · Marcello Esposito[5] · Francesca Morgante[6] · Giovanni Abbruzzese[7] · Anna R. Bentivoglio[8] · Francesco Bono[9] · Mario Coletti Moja[10] · Giovanni Fabbrini[11] · Paolo Girlanda[6] · Leonardo Lopiano[12] · Claudio Pacchetti[13] · Marcello Romano[14] · Laura Fadda[1] · Alfredo Berardelli[11]

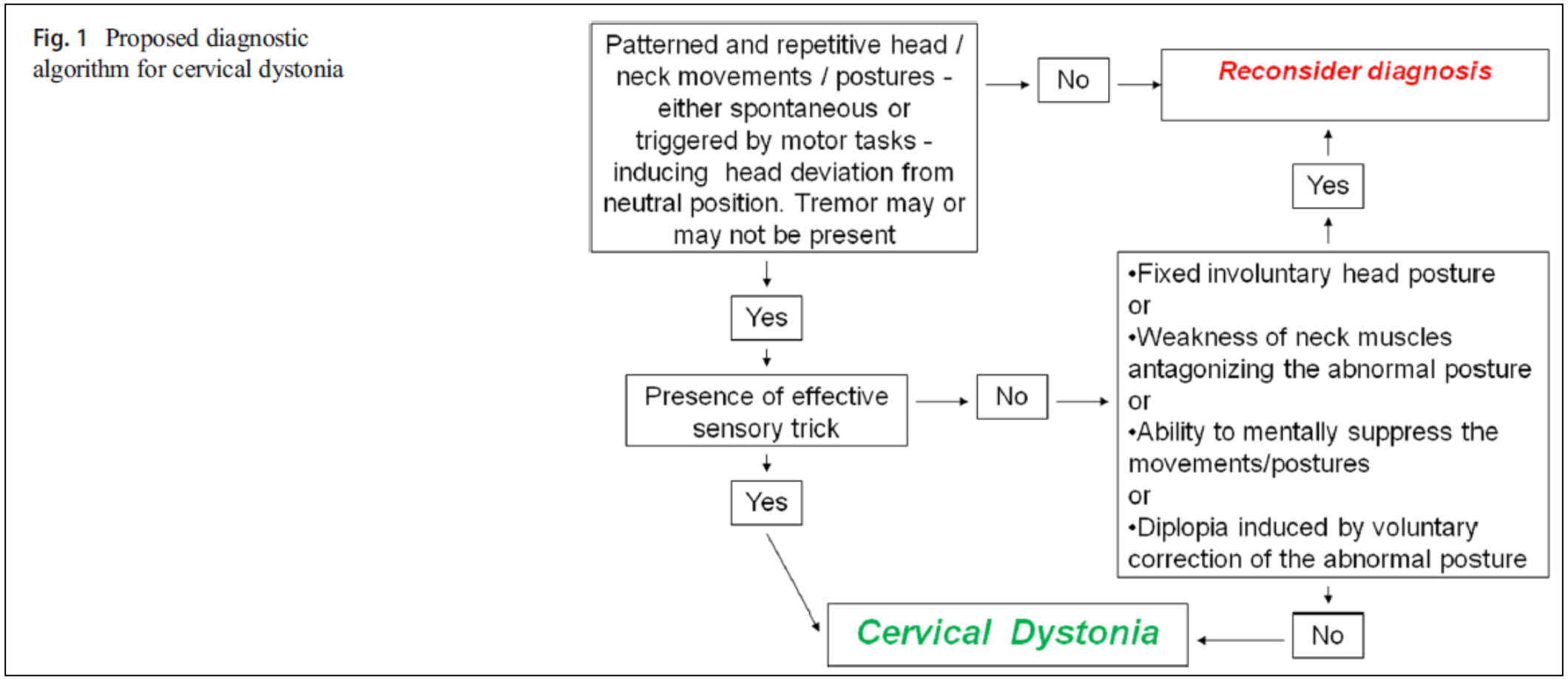

Fig. 1 Proposed diagnostic algorithm for cervical dystonia

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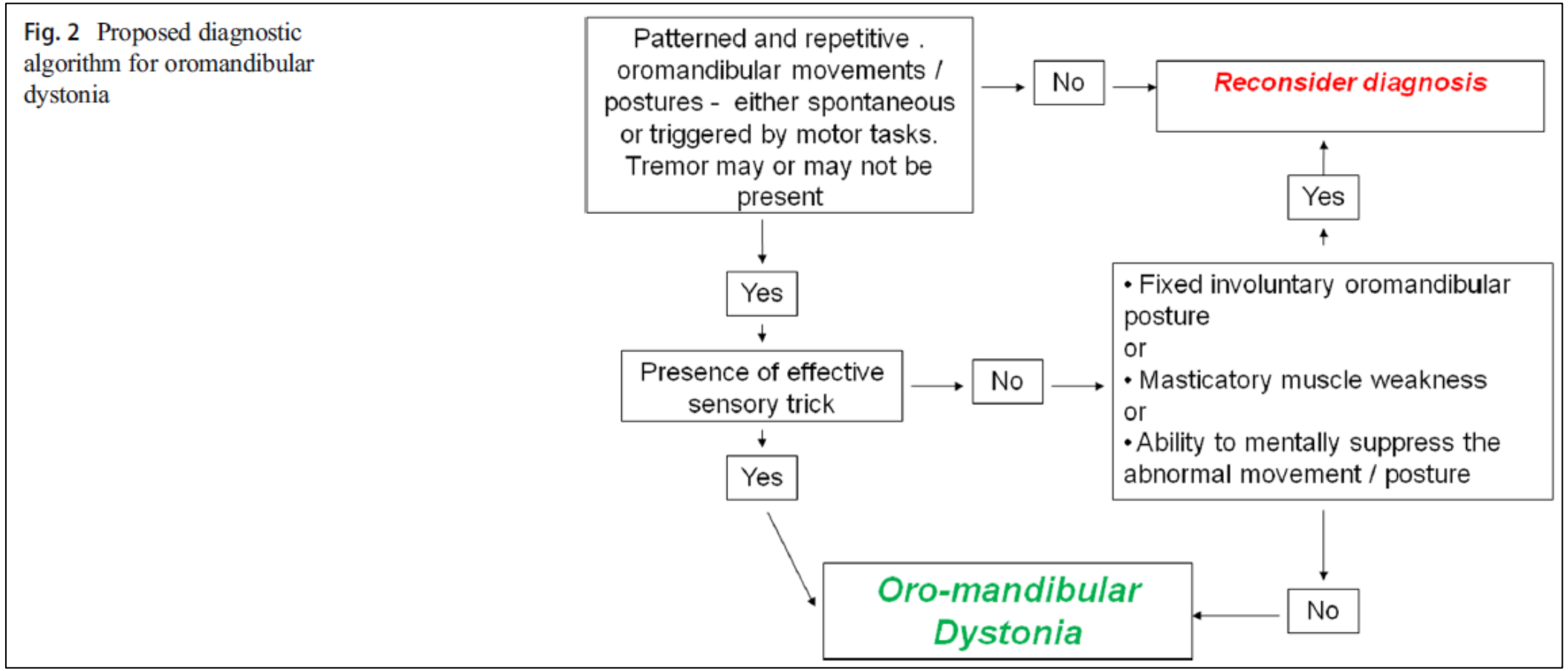

Fig. 2 Proposed diagnostic algorithm for oromandibular dystonia

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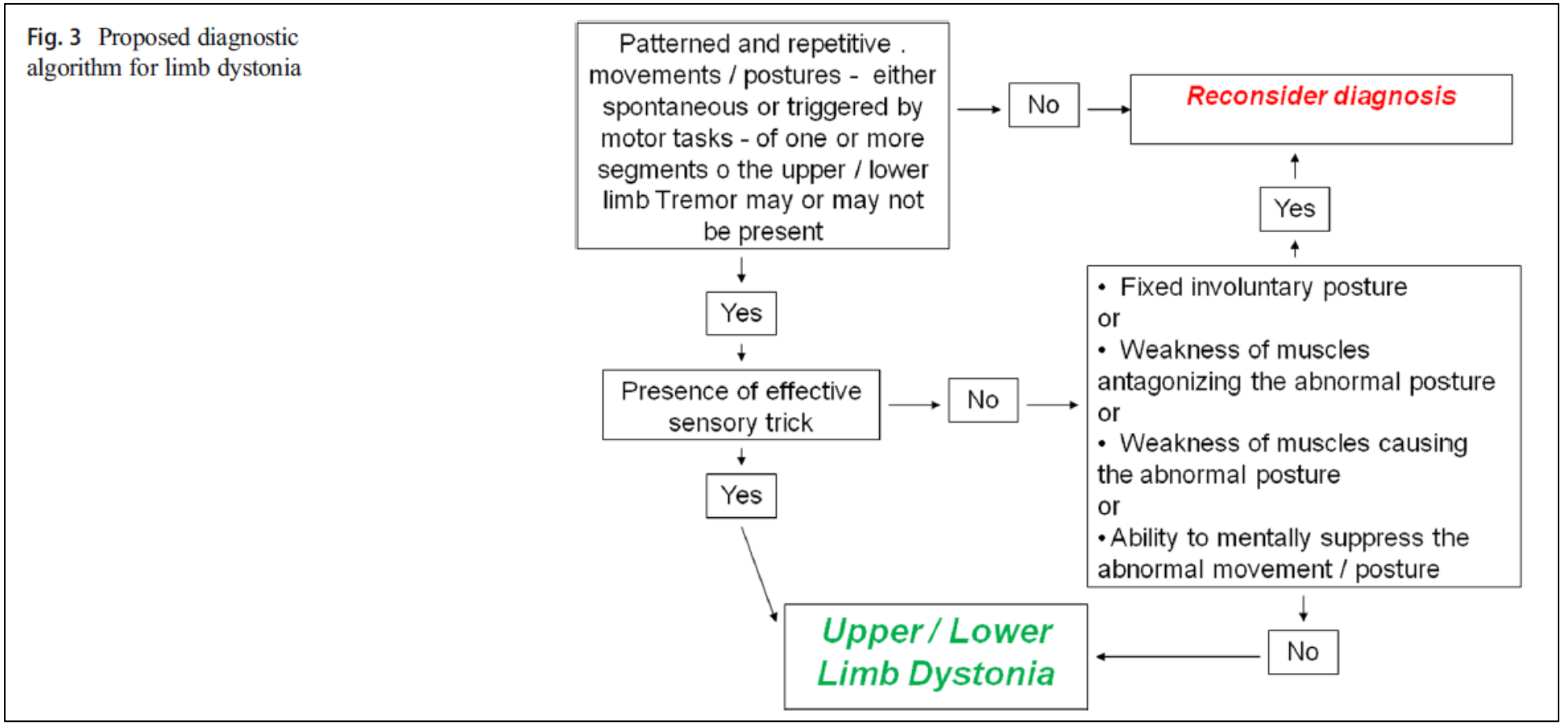

Fig. 3 Proposed diagnostic algorithm for limb dystonia

Conclusion

- More questions than answers
- Lumping vs. splitting
  - With lumping, there could be important differences that could weaken the results
  - With splitting, might be difficult to recruit “pure” cases
    - And then might not apply to real life
  - Spread is very common, so some lumping is inevitable
  - Compromise is necessary
- Diagnosis is not as easy as it first seems
- Algorithm development is a long process


LET'S
DISCUSS...