Can We Clearly Define Appropriate Patient Populations for Trials?

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Disclosure

No relevant conflicts of interest.
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

Brian D Berman, Christopher L Groth, Stefan H Sillau, Sarah Pirio Richardson, Scott A Norris, Johanna Junker, Norbert Brüggemann, Pinky Agarwal, Richard L Barbano, Alberto J Espay, Joaquin A Vizcarrondo, Christine Klein, Tobias Bäumer, Sebastian Loens, Stephen G Reich, Marie Vidalhiet, Cecilia Bonnet, Emmanuel Roze, Hyder A Jinnah, Joel S Perlmuter

How much are we willing to lump together?

Do primary adult-onset focal dystonias share aetiological factors?

Giovanni Defazio, Alfredo Berardelli and Mark Hallett

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
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

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. Ten experts opined about their validity. 4 features identified as possibly useful.

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 1**  
Content validity analysis testing the clinical phenomenology of blepharospasm

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

**Table 2**  
Sensitivity and specificity of clinical items scoring >0.5 on content validity ratio analyses in diagnosing blepharospasm<sup>a</sup>

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

<sup>a</sup>Data are percentages, and refer to the range of estimates obtained by 3 neurologists and 2 ophthalmologists.
Figure 2  Guideline for diagnosing blepharospasm

Presence of stereotyped, bilateral and synchronous orbicularis oculi spasms inducing narrowing/closure of the eyelids

No → Reconsider diagnosis

Yes

Presence of effective sensory trick

No → Increased blinking

Yes

Blepharospasm

Sensitivity 93%
Sensitivity 90%
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

<table>
<thead>
<tr>
<th>Item</th>
<th>Sensitivity/specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Spasms</td>
<td>95%/78%</td>
</tr>
<tr>
<td>2. Sensory trick</td>
<td>58%/94%</td>
</tr>
<tr>
<td>3. Increased eye closures</td>
<td>85%/50%</td>
</tr>
<tr>
<td>4. Inability to suppress</td>
<td>87%/52%</td>
</tr>
<tr>
<td>1 + 2</td>
<td>56%/98%</td>
</tr>
<tr>
<td>1 + 3</td>
<td>82%/84%</td>
</tr>
<tr>
<td>1 + 4</td>
<td>84%/84%</td>
</tr>
<tr>
<td>1 + (2 or 3) (algorithm of initial paper)</td>
<td>90%/82%</td>
</tr>
<tr>
<td>1 + (2 or 4)</td>
<td>88%/83%</td>
</tr>
<tr>
<td>1 + (2 or 3 or 4)</td>
<td>92%/79%</td>
</tr>
</tbody>
</table>
Expert recommendations for diagnosing cervical, oromandibular, and limb dystonia

Fig. 1 Proposed diagnostic algorithm for cervical dystonia

Patterned and repetitive head/neck movements/postures - either spontaneous or triggered by motor tasks - inducing head deviation from neutral position. Tremor may or may not be present.

Yes

Presence of effective sensory trick

Yes

Cervical Dystonia

No

Reconsider diagnosis

Yes

Fixed involuntary head posture or

Weakness of neck muscles antagonizing the abnormal posture or

Ability to mentally suppress the movements/postures or

Diplopia induced by voluntary correction of the abnormal posture
Fig. 2 Proposed diagnostic algorithm for oromandibular dystonia

Patterned and repetitive oromandibular movements / postures - either spontaneous or triggered by motor tasks. Tremor may or may not be present

- Yes
  - Presence of effective sensory trick
    - Yes
      - Reconsider diagnosis
    - No
      - Fixed involuntary oromandibular posture or masticatory muscle weakness or ability to mentally suppress the abnormal movement / posture

- No

Oro-mandibular Dystonia
Expert recommendations for diagnosing cervical, oromandibular, and limb dystonia

Giovanni Delfino, Alberto Albanese, Roberta Pellicciani, Cesa L. Scaglione, Marcello Esposito, Francesca Morgante, Giovanni Abbruzzese, Anna R. Bentivoglio, Francesco Bono, Maria Coletti Moja, Giovanni Fabbrini, Paolo Giuffrida, Leonardo Lupiano, Claudio Pacchetti, Marcello Romano, Laura Fadda, Alfredo Berardelli

Fig. 3 Proposed diagnostic algorithm for limb dystonia

- Patterned and repetitive movements / postures - either spontaneous or triggered by motor tasks - of one or more segments of the upper / lower limb. Tremor may or may not be present.

- Presence of effective sensory trick.

- Fixed involuntary posture or weakness of muscles antagonizing the abnormal posture or weakness of muscles causing the abnormal posture or ability to mentally suppress the abnormal movement / posture.

No

Reconsider diagnosis

Yes

Upper / Lower Limb Dystonia

No
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