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Declaration of Conflict of Interests

The authors declare no conflict of interest for this article.

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Introduction

Cervical radiculopathy (CR) is a relatively common neurological disorder caused by mechanical compression from a disc or other space-occupying lesion or from inflammation to the nerve root (Anekstein et al, 2012) The annual incidence of CR is 107.3 per 100,000 for men and 63.5 per 100,000 for women (Radhakrishnan et al, 1990). The clinical manifestations of cervical radiculopathy may include pain, sensory deficits, motor deficits, diminished reflexes, or combinations of these. Cervical radiculopathy typically is self-limiting with 75%–90% of patients achieving symptomatic improvement or resolution within a year with conservative care (Woods et al, 2015)

Although no gold standard exists as a reference standard for cervical radiculopathy, magnetic resonance imaging (MRI) is the preferred diagnostic method (Mink et al, 2003), since it can differentiate tumors, inflammation, visualize trauma, and the extensiveness of disc, arthritic, neural, and vascular cervical pathologies. Electrodiagnostic tests are capable of detecting clinically significant problems in many patients as well, although they are operator dependent and variable methods and normative values are used in practice (Reza Soltani et al, 2014). Furthermore it may be negative if performed before denervation has occurred or when re-innervation is complete (Ashkan et al, 2002). Cervical radiculopathy is considered a 'clinical diagnosis with imaging confirmation', and it is important to match valid clinical signs with MRI findings and/or electrodiagnostic test results (Carette and Fehlings, 2005 ; Kuijper et al, 2009).

There are numerous clinical tests used to diagnose cervical radiculopathy. Upper Limb neurodynamic tests ((ULNT) 1, 2a, 2b and 3), or also called upper limb tension test (ULTT), initially described by Elvey (Elvey, 1986), Butler (Butler, 2000) and Shacklock (Shacklock 1996), involve targeted sequences of movement that provoke mechanosensitivity of the nerve. The tests are performed by placing and releasing progressively more tension on the proposed

component of the nervous system that is being tested. A recent systematic review (Thoomes et al, 2017) concluded that "limited evidence for accuracy of physical examination tests for the diagnosis of CR" exists.

Moreover, neurodynamic test procedures in studies that populated the aforementioned systematic review used a variety of testing methods and results to determine a positive finding. Three criteria has been advocated when testing: 1) reproduction of neurogenic pain-burning or lightning-like pain, tingling sensation in the neck and arm (Apelby-Albrecht et al, 2012), the patient's symptoms reproduced (Wainner et al, 2003), or reproduction of pain (Ghasemi et al, 2013); 2) side to side range of motion difference (Wainner et al, 2003) or side-to-side difference in painful radiation (Apelby-Albrecht et al, 2012); and 3) increased/decreased symptoms with structural differentiation (Apelby-Albrecht et al, 2012) or cervical structural differentiation with cervical spine movement alone (Wainner et al, 2003). Interestingly, there is inconsistency in what is advocated to measure including conflicting evidence for reproduction of any pain or discomfort (Apelby-Albrecht et al, 2012 ; Ghasemi et al, 2013); and side to side range of motion comparisons (Nee et al, 2012). Most studies advocate the use of structural differentiation, which involves directional movement of a defined body region (e.g., neck side flexion) away from the area assessed to evaluate the effect of mechanical force on the nervous system and its impact on the patient's symptoms.

In clinical practice, many clinicians have assessed the accuracy of neurodynamic tests on two criteria as recommended by Nee et al (Nee et al, 2012) : 1) familiar patient's pain/symptoms reproduced and 2) increased/decreased symptoms with structural differentiation. Since we are unfamiliar with any studies that have included both findings in the assessment of CR, we investigated the accuracy of four ULNTs in comparison against a reference standard of medical history and MRI confirmation in patients with and without CR. We hypothesized that the findings may provide insight on the role of ULNTs (e.g., screening

or confirmation) and that the more rigid definition of a positive test should improve the specificity of the test findings. Further, combinations of test findings should result in more diagnostic accuracy than individual tests alone.

Materials and Methods

The study was a diagnostic accuracy study (prospective) design in which clinical testing occurred in a state of diagnostic uncertainty. The study followed the updated 2015 STARD reporting standards (Bossuyt et al, 2015). Patients were informed about the study and they gave their consent for participation before inclusion. The study was conducted in accordance with the Ethical principles and the Helsinki Declaration on research involving human subjects and was approved the French regulatory and ethics rules (n°2212189v0).

Participants were recruited from consecutive patients referred to a Neurosurgery Department by a general practitioner or specialist from September 2017 to September 2019. Each patient had a suspected neck disorder. Referred patients provided information and questionnaires about pain intensity and neck disability. To be included patients had to be aged 18 to 65 years, reporting arm pain with or without neck pain of at least 3-months in duration. In addition, they were required to have a self-reported pain score of at least 30mm and less than 80 on a 100 mm visual analogue scale (VAS) (Horn et al, 2016) during the previous 24 hours, and had a self-reported score of at least 20% on the Neck Disability Index questionnaire (NDI) (Masaracchio et al, 2013).

Subjects were excluded if they were unable to understand French, had suffered from a significant neck trauma at the time of the study (i.e., recent cranio-cervical trauma including cervical spine fracture), had a history of neck or arm surgery, inflammatory joint condition/arthritis, fibromyalgia, diabetes, pregnancy, cardiovascular, neurological, neoplastic or psychiatric pathology, cervical myelopathy, pyramidal or extrapyramidal pathology.

Reference Standard: The diagnosis of CR or a competing diagnosis was made by a single neurosurgeon with 15 years of experience from the consecutive patients included. Cervical radiculopathy is a clinical diagnosis that is confirmed through imaging verification, thus the diagnosis of CR was based on the following criteria: 1) history and presence of dermatomal radicular pain and/or symptoms (dysesthesia, muscle weakness or altered reflexes) attributable to a CR and 2) presence of MRI findings. MRI findings were specific in their confirmation of nerve root compression or irritation by disc herniation or stenosis in pre- or intra-foraminal space narrowing on the ipsilateral side and at the same or adjacent level of radicular pain (Kuijper et al, 2008). The reference standard results were interpreted without knowledge of the results of ULNT.

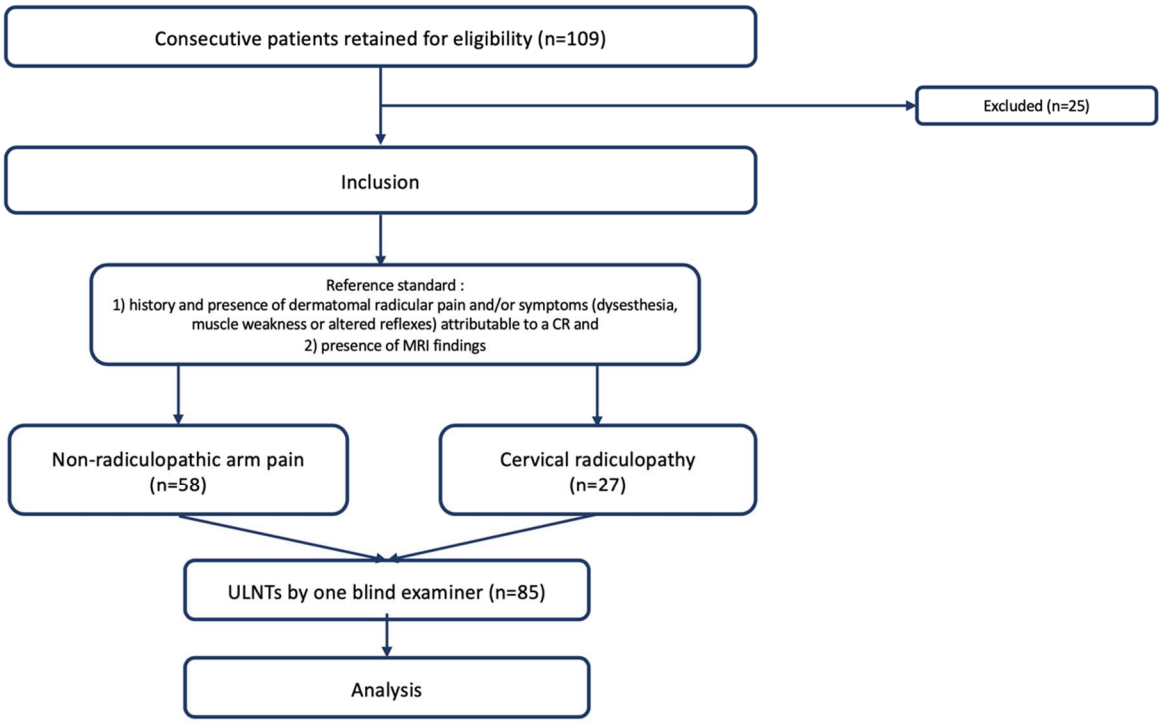
Index tests : Approximately one hour after the reference standard was provided by the neurosurgeon, a single physiotherapist with 10 years of experience in neck pain management, and advanced certification for orthopedic assessment evaluated the ULNT on each participant. No intervention was allowed between the index test(s) and reference standard. The physiotherapist was blind to the patient history, clinical/MRI findings and the diagnosis. The index test results were interpreted without knowledge of the results of the reference standard and the presence of CR. Before the tests, patients were instructed to communicate the onset of any sensation such as stretch, tingling or pain anywhere in the arm or neck (Schmid et al, 2009). The patient was positioned supine without a pillow (Walsh 2005). The examiner performed the ULNTs for that are purported for the median (ULNT1 and ULNT2a), radial (ULNT2b) and ulnar (ULNT3) nerves (Figure 1) in randomized order using randomization software. Upper limb neurodynamic testing was operated according to the standardized sequence previously described (Butler, 2000; Nee et al, 2012 ; Schmid et al, 2009), with a 5-minute break between each test to avoid any pain sensitization by repeating tests (Walsh

2005). Passive movements were achieved to the end of range or until symptoms were produced (Schmid et al, 2009). The non-symptomatic side was tested first for each ULNT for familiarization with sensation/pain induced by tests. A ULNT was considered as positive if both of the two following criteria were met:

- Reproduction of a familiar symptomatic complaint of arm pain and/or neck pain at least partially (pain or dysesthesia including burning, or lightning-like pain, or tingling sensation) (Nee et al, 2012);
- Structural differentiation: Once such a familiar complaint was provoked, structural differentiation between neurogenic and non-neurogenic sources was performed by the addition of sensitizing movements at a site distant to the pain: ipsilateral- or contralateral cervical lateral flexion, elbow or wrist extension/flexion, or shoulder girdle elevation (Appendix A) (Nee et al, 2012);

Tests were considered negative if each failed to meet the positive criteria identified above or indeterminate if the patient was unable to tolerate the test of position to allow complete execution of the test.

Figure 1. Flow chart



Results

Statistical analysis were carried using SPSS (IBM SPSS, Version 26.0. IBM Corp. Armonk, NY). Variables normality was tested with Shapiro-Wilk test for continuous data. Nonparametric continuous variables were described as medians and interquartile ranges and differences were tested using the Wilcoxon Mann Whitney test. Gaussian variables were described with means and standard deviations and differences were tested using the Student's t-test. Categorical variables were described as numbers and percentages. They were compared using Chi square test or Fisher's exact test, as appropriate. P-value significance level was set at .05 and all tests were bilateral. Two by two tables were created for each ULNT measure. ULNT test performances were analyzed using calculations for sensitivity, specificity, positive likelihood ratios (LR+), and negative likelihood ratios (LR-). Sensitivity is the percentage of people whose test is positive for a specific disease among a group of people who have the disease (Cook et al, 2020). Specificity is the percentage of people whose test is negative for a

specific disease among a group of people who do not have the disease [22]. LR+ are the probability of a person with the disease testing positive divided by the probability of a person without the disease testing positive (Cook et al, 2020). LR- are the probability of a patient who has the condition of testing negative divided by the probability of a patient without the disease, testing negative (Cook et al, 2020).

We also calculated pretest probability, which is the probability of the condition being present before the diagnostic result is known and is sample specific for those enrolled in our study, and post-test probability with a positive and a negative finding on the ULNTs. Post-test probability is the percentage chance of the condition being present after a positive or negative finding for a ULNT. Generally, a positive test will increase the post-test probability of diagnosing the condition (otherwise known as ruling in the diagnosis). In contrast, a negative finding will generally decrease the post-test probability of diagnosing the condition (otherwise known as ruling out the condition) (Cook et al, 2020).

We calculated sensitivity/specificity, LR+/LR-, and post-test probabilities with a positive and a negative finding for the four individual ULNT tests and combinations of these tests. When calculating combinations of findings, the clusters of tests were placed in "conditions" (e.g., 1 of 4 is positive, 2 of 4 is positive, etc.) and evaluated for their abilities to influence post-test probability change with each defined condition. For all analyses, we also evaluated post-test probability change, which is the difference between the pre-test prevalence and the post-test finding with a positive or a negative result (Cook et al, 2020). Since the purpose of a test is to change the post-test probability of an accurate diagnosis, larger post-test probability changes were considered to have the highest clinical utility. 95% confidence intervals (95%CI) were calculated for all of these features.

Between September 2016 to December 2018, 85 participants, from 109 individuals

who were screened, were enrolled in the study. Of the 85 participants, 27 (31.7%) were diagnosed with CR, 42 with neck and non-radiculopathic arm pain, 12 with peripheral nerve entrapment, and 4 with diffuse shoulder pain (Table 1). All participants received the same reference standard and were included for analysis (Figure 1). Diagnostic accuracy of the four individual ULNTs are presented in Table 2. All four of the tests were more specific, than sensitive, with the ULNT3 demonstrating the highest specificity. None of the four tests markedly influenced post-test probability with a positive or a negative finding, with post-test probability changes from baseline prevalence ranging from 41.58% with a positive for ULNT3 to 15.72% with a negative for ULNT 2a.

Table 1: Baseline characteristics of the subjects (n=85)

	Cervical radiculopathy	Non-radiculopathic arm pain	
Age*	43.96 (8.94)	45.27 (9.74)	p = 0.61
Height (m)	1.66 (0.09)	1.67 (0.08)	p = 0.54
Body Mass Index *	24.73 (3.91)	24.88 (4.97)	p = 0.74
Duration (self-report) in months *	93.25 (98.41)	70.51 (62.31)	p = 0.69
Visual Analogue Scale for Pain*	5.14 (1.58)	5.03 (1.53)	p = 0.73
Neck Disability Index (%)	38.16 (14.14)	43.07 (13.90)	p= 0.19

Table 2: Diagnostic Accuracy of Individual Upper Limb Neurodynamic Tests. Pre-test Prevalence = 31.7%.

	Sensitivity	**Specificity**	**LR+ (95% CI)**	**LR- (95% CI)**	**Post-test Probability**	**Post-test Probability with**

					with a Positive Finding (95% CI)	a Negative Finding (95% CI)
ULNT 1	59.26 (38.80, 77.61)	75.86 (62.83, 86.13)	2.46 (1.41-4.27)	0.54 (0.33-0.87)	53.30 (39.55-66.46)	20.04 (13.28-28.76)
ULNT 2a	70.37 (49.82, 86.25)	72.41 (59.10, 83.34)	2.55 (1.57-4.14)	0.41 (0.22-0.75)	54.20 (42.15-65.77)	15.98 (9.26-25.82)
ULNT 2b	55.56 (35.33, 74.52)	75.86 (62.83, 86.13)	2.30 (1.30-4.06)	0.59 (0.38-0.92)	51.63 (37.63-65.33)	21.49 (14.99-29.92)
ULNT 3	40.74 (22.39, 61.20)	93.10 (83.27, 98.09)	5.91 (2.07, 16.87)	0.64 (0.46-0.88)	73.28 (48.99-88.65)	22.95 (17.59-28.99)

Diagnostic accuracy of test conditions for combinations of ULNTs are presented in Table 3. Characteristically, with lower conditions (e.g., 1 of 4 is positive) values exhibit high sensitivity and low specificity, whereas higher conditions (4 of 4 are positive) values exhibit low sensitivity and high specificity. As expected, the condition of 1 out of 4 ULNT tests positive was the most sensitive combination whereas the condition of 4 out of 4 ULNT tests was the most specific. The condition of 1 out of 4 tests positive has the ability to "rule out" CR (LR-=0.08), exhibiting a post-test probability change of 28.12% with a negative finding. The condition of 4 of 4 tests positive had an infinite LR+ but there were only 3 cases in which all four tests were positive. The condition of 3 of 4 tests positive occurred in 12 of the 27 patients with CR and provided a LR+ of 12.89 and a post-test probability of 85.71 (post-test probability change of 54.01%). No adverse events from performing the index test or the reference standard were observed.

Table 3. Diagnostic Accuracy of Clustered Upper Limb Neurodynamic Test findings (Conditions). Pre-test Prevalence = 31.7%.

	Sensitivity	Specificity	LR + (95%	LR- (95% CI)	Post-test Probability	Post-test Probability with

			CI)		with a Positive Finding (95% CI)	a Negative Finding (95% CI)
1 of 4 Positive	96.30 (81.03, 99.91)	46.55 (33.34, 60.13)	1.80 (1.40, 2.32)	0.08 (0.01, 0.56)	45.51 (39.38-51.84)	3.58 (0.46-20.62)
2 of 4 Positive	85.19 (66.27, 95.81)	74.14 (60.96, 84.74)	3.29 (2.07, 5.23)	0.20 (0.08, 0.50)	60.42 (48.99-70.82)	8.49 (3.59-18.83)
3 of 4 Positive	44.44 (25.48-64.67)	96.55 (88.09-99.58)	12.89 (3.10-53.62)	0.58 (0.41, 0.81)	85,71 (59.06-96.14)	23.237 (18.57-28.82)
4 of 4 Positive	11.11 (2.35, 29.16)	100.00 (93.84, 100.00)	Inf.	0.89 (0.78. 1.02)	100	29.23 (26.58-32.13)

Discussion

This study sought to determine the diagnostic accuracy of four ULNTs in identifying CR in comparison with a reference standard of clinical diagnosis with MRI confirmation. The study was performed in a situation of diagnostic uncertainty and used a more rigid definition of what constitutes a positive test compared to previous studies [12-14]; the tests also more closely matched how the tests are used in clinical practice. Findings were that ULNTs when used in isolation did not lead to acceptable LR-, LR+ or post-test probability. However, 3 out of 4 tests positive can rule in CR with a LR+ of 12.89. One of four positive tests provided a LR- of 0.08 indicating that CR can be ruled out if no tests are positive. Of the four tests, the ULNT3 influenced post-test probability the most with a positive test (73.28%), whereas the ULNT2a influenced post-test probability the most with a negative test (15.98%).

Each ULNT provided stronger LR+ values than LR-, thus influencing post-test probability with a positive finding more notability than a negative finding. Our findings are markedly different than those from Wainner et al. who found very low values of LR+ (<1.3) - suggesting that they did not rule in - and moderately low LR- values (>0.12) - suggesting

224 they are better for ruling out (Wainner et al, 2003). Ghasemi and colleagues [14] failed to
225 report a LR+ (or a LR-) (Ghasemi et al, 2013) and our calculations from their sensitivity and
226 specificity values yielded LR+ values similar or worse than those of Wainner and associates
227 (Wainner et al, 2003). The differences in findings compared to those of others (Wainner et
228 al, 2003 ; Ghasemi et al, 2013) are likely related to the way we defined a positive index test
229 (familiar compliant that was altered by structural differentiation). In Wainner and
230 colleagues' study, an ULNT was defined as positive if only one of the following criteria
231 were present: reproduction of the patient's symptoms, or side to side range of motion deficit,
232 or structural differentiation using the cervical spine (Wainner et al, 2003). Ghasemi et al.,
233 reported a positive finding if 'pain' occurred during testing (hasemi et al, 2013). Basing the
234 test outcome on one criterion alone as identified by those authors could lead to an increase
235 in false positive findings, thus decreasing specificity, and worsening the LR+ value
236 (Schiffman et al, 2014). Apelby-Albrecht et al. defined as positive if all the three following
237 criteria were met: reproduction of neurogenic symptoms according to a dermatomal pattern,
238 increased or decreased symptoms with structural differentiation, and a difference in painful
239 radiation between sides (Apelby-Albrecht et al, 2013). Our LR+ values are very similar to
240 previous findings by a recent systematic review (Thoomes et al, 2017) calculated from data
241 reported by Apelby-Albrecht et al (Apelby-Albrecht et al, 2013). However, in our study
242 ULNT was defined as positive according to two criteria and we include a more mixed
243 control group population (58 neck or shoulder pain, thoracic outlet syndrome and carpal
244 tunnel syndrome) than Apelby-Albretch (only 18 subjects with neck pain or carpal tunnel
245 syndrome) (Apelby-Albrecht et al, 2013). These findings highlight the importance to
246 clinicians of determining a positive ULNT based on symptom reproduction together with the
247 effects of structural differentiation, at least in diagnosing cervical radiculopathy.

In their recent systematic review of diagnostic tests for CR, Koulidis et al [25] concluded that ULNTs could only be used as a "ruling out" strategy (Koulidis et al, 2019) based on Apelby-Albrecht et al's data (Apelby-Albrecht et al, 2013). Conversely, in our sample, ULNT when used in isolation were better at ruling in CR versus ruling out, yet clustering the ULNT findings produced large changes in post-test probability with either a negative finding or a positive finding. The condition of one of four positive tests yields a LR- of 0.08 (95%CI=0.01-0.56). This means that when none of the four ULNTs are positive it can rule out CR with only a 3.58% chance that the patients in this sample had CR. Moreover, using multiple combination of ULNT demonstrated that the condition of 3 of 4 positive tests yielded a LR+ of 12.89 (95%CI=3.10-53.62) which means it can rule in CR with a post-test probability of 85.71%. We recommend the use of 3 of 4 conditions over 4 of 4, since this finding was uncommon and because the confidence intervals crossed 1.0 for the LR- analyses.

We are also the first to report post-test probability of a positive and negative finding with an ULNT, an analysis omitted from past works (Apelby-Albrecht et al, 2013; Ghasemi et al, 2013). Post-test probability provides a better understanding of how markedly one's decision is influenced by single, or combined, positive or negative test results. This is of particular importance since the reporting of individual sensitivity and specificity values is not recommended (Hegedus and Stern, 2009 ; Baeyens et al, 2019) and may yield conflicting results for ruling in or ruling out conditions.

Study limitations

Although there is notable debate on an appropriate sample size for a diagnostic accuracy study (Hajian-Tilaki, 2014 ; Bujang and Adnan, 2016), we feel compelled to

identify our sample of 85 (including 27 CR) as a potential limitation. A smaller sample size may lead to less precision (e.g., wide confidence intervals). Only one clinician was involved in determining the reference standard and another was involved in determining the ULNT. Although the ULNT tester was blinded to the diagnosis of the patient, the transferability of their findings is unknown, since we did not test interrater agreement. Future research is needed to assessed the validity of ULNT with a larger sample of patients with CR and a larger control group with similar symptoms (thoracic outlet syndrome, neck/shoulder pain, peripheral nerve entrapment*, etc.*), and with more examiner and reference standards including magnetic resonance neurography and small fiber function (Schmid et al, 2013).

Conclusions

Our results support past findings that the singular use of ULNT to rule in or rule out CR is not recommended. When combinations are used, findings have higher clinical utility. When all ULNTs are negative, CR can be ruled out, whereas when 3 of 4 tests are positive, CR can be ruled in. As such, we recommend the use of ULNT tests as combinations only. Our study does not test the validity of ULNT tests for specific nerve trunks, which it is hypothesized to perform.

Table 1: Baseline characteristics of the subjects (n=85)
** Wilcoxon rank sum test*

Table 2: Diagnostic Accuracy of Individual Upper Limb Neurodynamic Tests. Pre-test Prevalence = 31.7%.

95%CI: Confidence interval at 95%
LR+: Positive likelihood ratio
LR-: Negative likelihood ratio
ULNT: Upper limb neurodynamic test

Table 3. Diagnostic Accuracy of Clustered Upper Limb Neurodynamic Test findings (Conditions). Pre-test Prevalence = 31.7%.

95% CI: Confidence interval at 95%
LR+: Positive likelihood ratio
LR-: Negative likelihood ratio

Appendix A. Standard sequence of joint movements and suggested structural differentiation maneuvers (sensitizing movements at a site distant to the pain) for each ULNT (Nee et al, 2012)

ULNT 1 (median nerve) :

- Shoulder girdle stabilization
- Shoulder abduction
- Wrist/finger extension
- Forearm supination
- Shoulder external rotation
- Elbow extension
- Structural differentiation:
  Cervical side bending or release wrist extension

ULNT 2a (median nerve) :

- Shoulder girdle depression
- Elbow extension
- Shoulder external rotation and forearm supination
- Wrist/finger extension
- Shoulder abduction
- Structural differentiation:
  Cervical side bending, or release shoulder girdle depression or release wrist extension

ULNT 2b (radial nerve) :

- Shoulder girdle depression
- Elbow extension
- Shoulder external rotation and forearm pronation
- Wrist/finger flexion
- Shoulder abduction
- Structural differentiation :
  Release shoulder girdle depression or release wrist flexion

ULNT 3 (ulnar nerve) :

- Wrist/finger extension
- Forearm pronation
- Elbow flexion
- Shoulder external rotation
- Shoulder girdle depression
- Shoulder abduction
- Structural differentiation :
  Cervical side bending, or release shoulder girdle depression or release wrist extension

Abbreviations :

CR : Cervical radiculopathy

ULNT : Upper limb neurodynamic tests

MRI : magnetic resonance imaging

LR+ : Positive likelihood ratio

LR- : Negative likelihood ratio

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