Algorithm for using SCI Electrodiagnostic Common Data Elements

The development of Spinal Cord Injury (SCI) Electrophysiological (EP) Common Data Elements (CDEs) is based on a long history of using electrophysiology to directly assess function within the nervous system. These methods have been validated and utilized in many neurological disorders besides SCI and several recent pre-clinical studies and clinical trials in SCI have used or are using some of these methods (see references with specific tests). As many therapeutic interventions in SCI are targeted to generate change in the nervous system to improve neurological function, and ultimately behavior, EP has many advantages as a method to detect, monitor and both qualify and quantify those changes. Most EP variables are direct measurements or relatively straight forward calculations and are usually continuous variables. They can be used to make simple assessments such as the conduction of neural signals through specific neuroanatomical pathways all the way to detailed measurements of complex neurological processes like the coordination of muscle activity across multiple muscles to execute movements or in response to sensory input. EP measures can detect subclinical changes, that is, those not detectable by a typical clinical exam, and may be used to track changes in neurological function before they might be detected by clinical or behavioral means. EP measures can often be characterized in SCI relative to those same variables measured in uninjured individuals so changes in the injured nervous system can be characterized as moving towards, or away from, normal neurophysiology. EP measures may also be useful, even retrospectively, in clinical trials to help explain “responders” vs. “non-responders” in terms of initial neurophysiological profiles to which the therapeutic intervention was applied or in terms of neurophysiological changes brought about by the intervention being tested. Finally, EP measures may help to explain the “why” underlying behavioral dysfunction in SCI. Is the subject walking slowly because of inadequate muscle activation or because of over-activation of inappropriate muscles (dyssynergia), either in terms of the timing or magnitude of that activation? Is an intervention generating multiple or mixed neurological effects such as both strengthening of muscle activations but also generating the development of dyssynergias?

There are, of course, limitations to the application of EP studies. They often require specific equipment or facilities that come with some costs. It is important to have technically trained and experienced staff to carry out data collection, trouble-shoot any technical issues that could confound that data collection and provide preliminary interpretation of the recordings made. It is often necessary to agree upon standardizing data recording, processing and analyzing procedures and to establish whether within lab or across labs reference or normal values are needed. It is also advisable to agree upon clinical circumstances where collecting EP data could be confounded by other neurological injury such as brain injury or peripheral nervous system injury or by treatments designed to alter neuronal activity such as pain or spasticity medications or sedating drugs. EP tests are more time intensive than many clinical or even some behavioral testing and are less commonly used, making the application of EP CDEs limited to relatively fewer centers than could execute clinical or behavioral testing. However, if EP CDEs become an important measure for preclinical study or a clinical trial, and investing in equipping, training and coordinating multiple research centers should be possible and useful. If one had, for instance, a therapy designed to improve re-myelination after SCI, investing in centers that carry out evoked potentials, and possibly training and equipping some additional centers to do so, could help answer the question as to whether the intervention is improving

signal conduction, even ahead of clearly demonstrated clinical or behavioral effect, something that might help the ongoing development of the intervention or lessen the number of test subjects needed to detect an effect.

EP measures can, at a first pass, be viewed as a neurophysiological way to characterize the “phenotype” of the SCI and to detect if there is neuropathology beyond the SCI. While all would agree that damage to the dorsal or ventral horn of the spinal cord would constitute SCI and plexus or peripheral nerve injury would constitute peripheral nervous system injury, damage to the dorsal or ventral roots within the spinal canal might be characterized either way, regardless of whether the same dorsal root ganglion neuron or motoneuron populations could be affected in any of these three anatomical locations. Traditional peripheral nerve conduction testing and electromyography can fairly well characterize radiculopathy, plexopathy and peripheral neuropathy and a battery of imaging, clinical scales and neuropsychiatric testing can characterize the extent and nature of brain injury that might be associated with SCI. These confounders, of course, would influence the interpretation of SCI EP testing. Once the presence or absence of these confounders is known, EP testing then can help characterize the SCI itself, testing the integrity of certain signal conduction pathways to establish a cross-sectional characterization of the SCI and testing multiple segmental levels of spinal cord function to establish a rostral/caudal extent of the injury. These measures can be compared to imaging results from CT or MRI to establish a better understanding of how anatomical injury and physiological injury relate.

Beyond an initial “phenotyping” of the SCI, EP measures can be used to test two major aspects of neurological functioning in SCI, namely conduction of signals and processing of those signals on either side of the injury site. Characterizing conduction or “what can get through the injury” does not necessarily describe how residual trans-injury pathways are actually used by the remaining nervous system after SCI, nor the “value” of the signals that do get conducted. Nevertheless, understanding which pathways are partially preserved after injury, and testing the sensory modalities or motor function they subserve, is an important part of understanding the SCI and these may be good detectors of improved signal transduction following an intervention designed to improve that function (strategies to remyelinate, regenerate long distance connections, or even augment sprouting in residual pathways).

Ascending sensory pathways can be characterized in several ways including dermatomal somatosensory evoked potentials (dSSEPs) designed to test dorsal column function and contact heat evoked potentials (CHEPs) designed to test spinothalamic pathways. These two tests involve stimulating and recording signals across the level of SCI. Electrical perceptual thresholds (EPT) test perception of sensory stimuli provided at different dermatomes and represent a combination of EP stimuli and subjective subject reporting. Quantitative sensory testing (QST) also tests sensory perception but without neurophysiological stimulation or recording; these tests are included in the EP CDEs in the interest of completeness and their not being included in other SCI CDE data sets. Descending motor pathways can be characterized with motor evoked potentials (MEPs) which depend most heavily on corticospinal pathways. Central motor conduction time testing can also be accomplished using MEPs. Central sensory

conduction time testing can be done using SSEPs but not CHEPs due to the slower stimulus application times and delay in activating peripheral sensory receptors for nociception.

The processing of signals that do pass through the level of SCI is probably responsible not only for the neurophysiological output of the below-injury spinal cord but also for altered supraspinal activity following SCI. Despite the importance of this, EP testing of signal processing in SCI, either above or below the SCI, has remained less explored than studies of conduction. Perhaps one of the more published methods which quantitatively characterizes the coordination of muscular activation below the level of SCI under a variety of test conditions and can evaluate the presence of supraspinal influence over below-injury spinal neural circuitry has been the brain motor control assessment (BMCA). As such, the BMCA has been included in the current set of SCI EP CDEs. Other measures of spinal cord processing have been studied, including Hoffman (H) reflexes, posterior root muscle reflexes (PRMRs), and cutaneous reflexes such as tibial reflexes and withdrawal reflexes (BMCA), tested both at rest and with conditioning stimuli or during motor tasks to evaluate their modulation. While these have provided important insights in recent human studies, they are not yet currently widely applied in clinical study. It is anticipated that these reflexes could be the next set of EP measures to be developed for clinical study and for inclusion in the next version of SCI EP CDEs. Studies of altered signal processing at supraspinal levels (altered processing of ascending signals or altered organization of descending commands) has just now become an interest of a wider group of SCI neurophysiologists but this often needs to be combined with functional imaging. That is to say, electroencephalography (EEG) for sensory evoked potentials has good temporal resolution but relatively poor anatomical resolution of signal processing and functional magnetic resonance imaging (fMRI) has the opposite. Finally, beyond sensory and motor testing, some aspects of autonomic function can be tested using EP measures. Sympathetic skin responses (SSRs) have been included in the SCI EP CDE but these should probably be considered with non EP testing of autonomic measures such as heart rate, blood pressure and further measures such as quantitative testing of bowel and bladder function.

The choice of which SCI EP CDEs to be used in a specific study should be made based on a spectrum of considerations beyond those specific to the techniques themselves. Some of these considerations include the level of SCI, the severity of the injury and the age of the SCI. For high cervical (C1-C4) or mid thoracic (T2-L1) injuries, it may suffice to characterize conduction of signals through the injury site (although the BMCA is developing an assessment of respiratory motor control that depends on some thoracic spinal cord levels). At cervical (C5-T1) or lumbar/cauda equina (L2-L5 injuries) it will be more important to use EP methods to characterize not only the degree of disconnection between spinal neural circuits below the injury and supraspinal centers above it, but also the extent of muscle denervation, sensory de-afferentation, and lost function or modulation of segmental interneuronal physiology (altered processing functions). Current clinical exams and behavioral tests cannot well characterize the combination of these problems that may be leading to disability but EP measures can begin to tease these apart, something that could be of use in prospectively grouping patients based on their neurophysiological “phenotype” ahead of a study or in retrospectively interpreting differences between “responders” and “non-responders.”

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The use of EP testing is probably appropriate in all severities of SCI, especially in light of its ability to detect subclinical neurophysiology, including the conduction of signals and the processing of those signals. The example of the SCI subject who is “complete” by clinical exam but “discomplete” by neurophysiological assessment (BMCA) is an important one. Even in clinically mild SCI, improvements in motor control (towards more normal neurophysiology) may be detected when some clinical or behavioral measures may have demonstrated a ceiling effect (achieving the best clinical score possible). As for the age of SCI, EP measures are probably appropriate for all durations of SCI. In fact, EP measures are regularly used for intra-operative monitoring during spinal surgeries immediately after injury and can be used to some extent even in unconscious patients (with the above mentioned caveats about other neurological injury and medication effects and taking into account the physiology of spinal shock). While it may be more difficult to carry out evoked potentials in the ICU than in outpatient rehabilitation, EP studies have been successfully conducted in the acute clinical setting and tracked recovery from that time point out to the chronic state.

The descriptions of the SCI EP CDEs here should serve as a starting point for understanding and applying those measures but clearly, electrophysiology in SCI is a dynamic and developing area of inquiry in SCI. While not always simple, it is an excellent means of assessing neurological function measured right at the level of the nervous system and it should significantly augment our understanding of SCI and its treatment when used in concert with clinical exams, behavioral testing, and even patient related outcomes.

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Guidelines for electrophysiology tests

Test Name: Nerve Conduction Studies and Electromyography (Peripheral Studies)

Outcome Measures: Motor Nerve Conduction Studies (NCS) and Electromyography (EMG) utilize muscular responses elicited by peripheral nerve stimulation or voluntary activation to test the motor final common pathway of the lower motor neuron (LMN). Motor NCS thus may be used to characterize spinal lesion by investigating the extent and severity of LMN damage at the lesion level as well as the state of spinal excitability (e.g. assessment of spinal shock). The combination of motor and sensory NCS may be used to detect additional peripheral nerve damage [1]. The combination of motor and sensory neurographic recordings allows for differentiation of muscle paresis due to spinal anterior horn cell (LMN)/anterior nerve root lesions or peripheral nerve damage (plexus, peripheral nerve)[2,3]. Detection of Compound Muscle Action Potential (CMAP) confirms the anatomical contiguity of the LMN innervation (including anterior horn cells of the LMN pool) to the targeted muscle and the amplitude and latency of the response provide indications of whether or not the peripheral conduction is impaired. F-wave(FW)-latency measures are needed for calculation of central conduction velocity in combination with MEP to further elaborate the conduction properties of the cortico-spinal tract [4].

Level/Severity of SCI: NCSs and EMG can be obtained in all patients (AIS A- E) and neurological level of injury (NLI) between C2-S3. They should preferentially be obtained in segments prone to have undergone LMN damage, i.e. median/ulnar nerve NCS and cervical segmental EMG for cervical NLI and peroneal/tibial nerve NCS and lumbar/sacral segmental EMG in low thoracit/lumbar NLI.

When can the test be applied? NCS and EMG can be used in any stage following SCI. There are no pharmacological interventions, anesthetics or metal instrumentation that would confound the results. In follow-up examinations any secondary development of motor nerve lesion due to spinal (myelomalacia, post-traumatic syringomyelia) or peripheral nerve damage (nerve entrapments) can be assessed in comparison with earlier assessments [1]. In the sub-acute stage, assessment of H-reflex and F-Wave recordings (FW) can be used to prove integrity of the proximal segment of the peripheral nerve and to document cessation of spinal shock and excitability of LMN [5,6].

Equipment needed: The basic equipment is a standard electromyographic recording system.

Costs: EMG/NCS machines are commercially available from $20k-$80k depending on specifications and the types of recordings to be undertaken. EMG needles and surface adhesive electrodes for NCS are $10 -$20 per assessment.

Training: Medical training or supervision is required as for clinical routine EMG/NCS examinations. (EMG/EP technologist / specialized neurophysiologist or neurologist MD).

Protocol: A complete NCS examination in SCI will usually include segmental EMG and reflex/FW examinations of several nerves. NCS uses focal electrical stimulation of peripheral nerves at standardized locations and recording (needle or surface electrodes) from standard

innervated muscles or proximal (orthodromic) or distal (antidromic) nerve points in sensory nerves. EMG uses concentric needle electrodes inserted into the muscle to detect MUP of one or several motor units for off-line evaluation.

Duration of Test: A complete NCS and EMG assessment requires 10 -20 minutes for any given nerve/segment. A full protocol includes bilateral assessment of 4 peripheral nerves/segments (40-60mins).

Measurements and their psychometric properties: NCS: Compound Muscle Action Potential (CMAP) will be reduced while sensory Nerve Action Potential (sNAP) remains unchanged in case of spinal anterior horn cell or pure motor radicular damage. Motor and sensory Nerve Conduction Velocities (m/sNCV) are unaffected by SCI. FW persistence in combination with CMAP can help to distinguish spinal shock from LMN damage. NCV (nerve conduction velocity) and FW-latency are needed to exclude peripheral conduction slowing. EMG: Pathological spontaneous activity of the motor unit is known as a sign of LMN damage. A quantitative analysis of motor unit potentials (MUP) indicates normal, chronic or acute neuropathic alteration of the investigated nerve/segment and can detect axonal sprouting during the process of peripheral nerve regeneration.

Data Analysis: Standard descriptive and inferential statistics can be applied to the raw peak-to-peak CMAP amplitude measures and conduction times/velocities. FW latencies are largely dependent on the physical stature of the individual (height) and adjustment for height needs to be applied. CMAP amplitudes are more variable between subjects than side differences within a subject. EMG data can only be used in a descriptive way.

Data Interpretation and pitfalls: Loss of FW and CMAP amplitude reduction at the lesion level reflects the extent of spinal motoneuron cell damage. However, when applied very early (< 10 days) after SCI they may not reflect LMN damage due to incomplete Wallerian degeneration at this time point. However, dependent on the severity of SCI peripheral motor axons below the level of the lesion exhibit severe degeneration which is likely the result of transsynaptic degeneration [7,11]. There is partial, although significant, recovery of CMAP during the second half year following SCI [7]. These changes have to be considered when utilizing CMAP to assess LMN damage in conjunction with SCI.

Relationship to other tests: CMAP amplitudes may be used in conjunction with MEPs to calculate a ratio of central over peripheral stimulated CMAP. FW latency is required to rule out peripheral slowing in the process of measuring central conduction times (see Guidelines on MEP). There have been descriptions of the relationship of NCS in the upper extremity and hand function[12]**.**

Clinical status: NCS and EMG are widely used clinically in the assessment of a number of neurological disorders involving peripheral nerves, plexus, radicular lesion and the spinal cord. Secondary development of motor nerve lesion due to spinal (myelomalacia, post-traumatic syringomyelia) or peripheral nerve damage (nerve entrapments: NCV slowing or local CMAP amplitude reduction as an indication of conduction block) can be detected and quantified by means of NCS tools and their combination with EP techniques. In order to define the

pathophysiology of SCI it is most important to assess the extent of spinal segmental motoneuron damage which will be reflected as CMAP amplitude reduction and/or denervation activity in the segmental EMG, and which corresponds to peripheral muscle atrophy. Generally, NCS is able to detect and distinguish peripheral nerve damage which may affect clinical and functional outcome but which is unrelated to SCI.

Classification: Supplemental

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Test Name: Quantitative Sensory Testing (QST)

The most current forms of Quantitative Sensory Testing , which involve application of computer controlled thermal or vibratory stimulation and psychophysical scaling against established norms, are emerging as important adjuncts to clinical evaluation of sensory function and pain in SCI Finnerup et al 2003;2004; Felix and Widerström-Noga 2009; Savic and Nicotra 2007; Hayes et al 2003; Cruz-Almeida et al 2012. Detection of perceptual thresholds for various thermal and vibratory modalities and the pain threshold to thermal stimuli enables discriminative evaluation of preserved sensory function and the differential involvement of spino-thalamic tract and the dorsal columns.

Outcome Measure: Thermal (cold and hot) perceptual and pain thresholds and vibratory perceptual thresholds, have been tested in individuals with SCI (Krassioukov, *et al*., 1999; Hayes, *et al*., 2002; Finnerup, *et al*., 2007; Felix and Widerstrom-Noga, 2009). The aim of QST is to provide additional insights into clinically “impaired” sensation, as well as to sensitivity to detect impairment in “normal” dermatomes near or above the level of lesion (i.e., sub-clinical deficits).

Level/Severity of spinal cord injury (SCI): QST can be applied across most dermatomes (C2-S3), in individuals with sensorimotor complete/incomplete injuries.

When can the test be applied? QST could be applied at any time-point after injury, however it does requires that the subject report the intensity of stimulation and thus may be difficult to measure in the very acute phases of injury.

Equipment needed: A computer-driven device capable of delivering graduated hot or cold stimuli through Peltier elements to a contact plate in the thermode or graduated vibratory stimuli through an electro-magnet driven vibrating head, is necessary for the controlled application of stimuli. Temperature changes are typically monitored through a thermistor in the hand held unit.

Costs: The standard device used to acquire QST thermal or vibratory thresholds costs approximately $40k .

Training: A short period of technical training is required. Most health care professionals or scientists would acquire competent and reliable skills with several days of supervised training by a neurologist. An experienced clinician or scientist is required to interpret the data.

Protocol: Typically, perceptual and pain thresholds are assessed by slowly increasing the intensity of stimulation at a set rate from baseline until the individual verbally reports a change in sensation – the so called ``method of limits``. The verbal reporting departs from techniques used by clinicians with other disorders because of the limited hand function of many SCI patients. To ensure the attention of the subject, testing should be performed in a quiet, temperature-controlled room. Before beginning testing, subjects should be read standardized instructions with regards to reporting detection and pain thresholds. An area suspected of having normal sensation (i.e., well above the level of injury) should be tested first. Perception thresholds should be examined before pain thresholds to avoid an interaction of stimulation order. An average of three consecutive runs should be applied for determination of thresholds.

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The method of limits can be adopted in a shorter time frame, and is considered as accurate as other threshold measurements (i.e. method of levels). For detection of thermal perception and pain thresholds an increase of temperature less than $1^{o}C/s$ is advisable. To standardize stimulation location, dermatomal boundaries used by the International for the Neurological Classification of SCI should be employed.

Duration of the test: The duration of the test depends upon the number of dermatomes examined. With instructions, each dermatome may take approximately 5 minutes for examination of perceptual and pain thresholds. a similar length of time is required for detection of vibratory stimuli.

Measurements and their psychometric properties: In general, the construct validity of QST outcomes has been demonstrated with other measures of sensory function, including the ISNCSCI and electrophysiological measures of preserved sensation (Hayes, *et al*., 2002). Depending on the dermatome examined and the modality tested, higher day-to-day variability has been reported in SCI subjects, suggesting the requirement for multiple measurements to establish reliable QST baseline measures (Krassioukov, *et al*., 1999). In other reports, the intraclass correlation coefficients for mechanical, vibration, warm, and cool detection thresholds were in the "substantial" range, while thresholds for cold pain and hot pain demonstrated "fair" stability in this sample of patients (Felix et al 2009). While most individuals with sensorimotor complete injuries will have no perception or pain thresholds, there is some evidence of sensory dyscomplete injury based on QST thresholds (Finnerup et al 2004; Hayes etal 2002). Reference data exist for able-bodied control subjects but there is value to establishing normative control values on an individual lab basis.

Data Interpretation: The absence of sensation is denoted by no apparent perception or report of pain threshold greater than $50^{o}C$ (warm, hot pain) or less than $0^{o}C$ (cold, cold pain). The determination of Z-scores has proven useful for standardized comparison with healthy control values. It is important to establish whether the patients are taking any analgesic or central depressant medications that might influence the interpretation of pain threshold.

Relationship to other tests: Thermal QST provides a comprehensive analysis of the spino-thalamic tract function while vibratory thresholds appear to reflect dorsal column function. QST has been examined with other measures of sensory function including SSEPs and standard clinical exam.

Clinical status: The most widespread application of QST in SCI at present is for the assessment of neuropathic pain. Studies examining the responsiveness of QST during recovery from SCI have not been performed.

Evaluation: QST is used clinically and experimentally and in the hands of experienced clinician-scientists.

Classification: Supplemental

References

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Test Name: Electrical Perceptual Thresholds (EPTs)

Purpose of Test: The Electrical Perceptual Threshold (EPT)[1] test provides a quantitative measure of cutaneous perception that can be applied to all individual dermatomes. The test was developed as an adjunct to the clinical neurological assessment of cutaneous sensory testing embodied in the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) (light touch (LT) and pin-prick (PP) tests)[2].

Level/Severity of spinal cord injury (SCI): The EPT can be used in patients with any degree of injury (AIS A-E) and neurological level of injury (NLI) between C2-S3.

When can the test be applied? EPT can be used in the acute stage of spinal cord injury but does require the patient to respond verbally (can or cannot feel the stimulus). It can be used in the sub-acute and chronic states, again provided the patient can communicate verbally with the operator.

Equipment needed: The equipment required is an electrical stimulator capable of delivering repetitive square wave pulses with either manual or computer control of the current delivered in increments of ≤0.1mA up to a maximum of 10mA. If the electrical stimulator is to be controlled from a PC or laptop computer then a suitable data acquisition (DAQ) interface card is required. Disposable adhesive cathode electrodes and a re-usable metal plate electrode (anode) with strap are required.

Costs: Suitable electrical stimulators cost from $5k (manual control) to $10k (programmable, computer controlled, the latter requiring a DAQ card ($1-4k).

Training: A short period of technical training is required. Most health care professionals or scientists would acquire competent and reliable skills with several days supervised training by a neurologist. Informed interpretation of the EPT measures may require consultation with a spinal cord injury specialist neurologist.

Protocol: Subjects should be lying comfortably on a bed in a warm, quiet room throughout an EPT test. Electrical stimulation is delivered using a constant current electrical stimulator. The pulse characteristic should be a square wave (monophasic) current pulse with a width of 0.5 ms delivered at a repetition rate of 3 Hz. The maximum current should be set to 10 mA beyond which the EPT is considered undetectable. Stimuli are applied between an adhesive cathode electrode placed over the ASIA sensory key point of a dermatome and a second metal anodal plate electrode strapped on a remote location (arm or leg) distal to the cathode on the same side of the body. The conducting surface area of the cathode electrode should be approximately 380mm^2 (22mm diameter). Stimulation is generally described as feeling like a regular ‘‘light tapping’’ sensation at the location of the cathode and is never reported as painful. The conducting surface area of the anode electrode should be approximately 3x4cm. The large surface area minimises the chance of anodal break stimulation causing local sensation when higher stimulation intensities are used. Using the method of limits, the subjects should be asked to report immediately when they can first feel the sensation of regular ‘‘light tapping’’ as the intensity is raised from 0mA and then again when sensation disappears as intensity is lowered.

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The rates of ascent and descent should be set at 0.1mA per step increment after every third stimulus (approximately one step change in intensity per second). On reaching ascending threshold, the output should be increased by a further three increments of 0.1mA before reversing the change in intensity. When the subject reports a loss of sensation to the decrementing stimulus, the intensity is again logged (in mA). The procedure should be repeated three times for each dermatome[3].

Duration of Test: An EPT test of six dermatomes on both sides of the body takes approximately 30–40 min to perform.

Measurements and their psychometric properties: The threshold may be calculated as the mean of the three intensities logged on lowering the stimulus strength. These values are invariably lower than those recorded on raising the strength of stimulation. Published normative values for EPT for dermatomes C2-S3 are available[2, 4, 5]. EPT that exceeds the control mean value plus 2xSD of may be regarded as abnormally elevated. The procedure of averaging three estimates of EPT for each dermatome provides fair to good reliability for intra and inter-rater repeatability[3, 4, 5].

Additional Data Analysis: There is some evidence that normal EPT values depend on age and gender for certain dermatomes[1, 6].

Data Interpretation: There is a risk that patients provide early or late responses to stimulus applications, due either to conflicting stimulation (e.g. involuntary muscle twitch) or lack of attention. If a suspected case occurs (usually evident as an outlier) more than three repeat measures are recommended.

Relationship to other tests: There is evidence that the EPT corresponds to dorsal column (posterior column) function as assessed by the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) cutaneous test of sensibility through light touch (LT)[4, 7]. The EPT corresponds well with dermatomal somatosensory evoked potentials (dSSEP). Normal EPT equates to normal dSSEP, raised EPT delayed or pathological dSSEP and abnormal EPT to absent dSSEP[7, 8].

Clinical status: EPT has yet to be used widely in the clinical assessment of spinal cord injury and has not been used in other neurological disorders involving cutaneous sensory deficits. It has been used to reveal changes of cutaneous sensory function in the longitudinal progress of spinal injury and shown greater sensitivity than clinical neurological (LT) assessment[9, 10, 11, 12].

Evaluation: EPT provides a quantitative assessment of cutaneous sensory function mediated through the posterior column pathway.

Classification: Exploratory

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Algorithm for using SCI Electrodiagnostic Common Data Elements

Test Name: Sensory Evoked Potentials (SEPs), Including Somatosensory Evoked Potentials (Mixed and Dermatomal, mSSEPs and dSSEPs), Contact Heat/Laser Evoked Potentials (CHEPs/LEPs)

Outcome Measures: Amplitude and latency of prominent evoked potentials (EPs) recorded from the periphery, spine, and/or scalp recording electrodes. Depending on the site and modality of stimulation, prominent negative and positive peaks, averaged across multiple stimulations, are recorded for visual interpretation. Detection of SSEPs confirms the anatomical contiguity of large diameter fibers in the periphery, and conduction in the dorsal column. In contrast, LEPs and CHEPs reflect recruitment of small diameter afferents, primarily A-delta, and spinal conduction in the spinothalamic tract. For a comprehensive overview of SEP recommendations from the International Federation of Clinical Neurophysiology, please see Cruccu et al (2008).

Level/Severity of SCI: SEPs can be typically evoked in patients with sensorimotor incomplete injuries (AIS C, D and E). The detection of SSEPs will depend on the extent of damage in the dorsal columns, whereas the detection of CHEPs will depend on damage in the spinothalamic tract. In terms of assessing the level of injury, SEPs can be applied to individual dermatomes (C2-S3), thereby complementing the clinical examination of light touch and pinprick. Pudendal SSEPs can be employed to assess S4-S5 (i.e., lowest sacral segment). Based on anatomical differences between large and small diameter fibers after entering the spinal cord, CHEPs may be more sensitive than SSEPs to detect damage at the level of injury (Ulrich et al., 2013).

When can the test be applied? Like motor evoked potentials, SSEPs can be applied intra-operatively to assess conduction in ascending spinal cord pathways at earliest stage of SCI. In the acute stage, SSEPs are particularly useful to confirm the completeness of injury and predict future functional outcomes (Curt & Dietz, 1999, Iseli et al., 1999, Kuhn et al., 2012). Later clinical applications include the use of SEPs as a complementary tool to neuroimaging in cases of worsening neurological condition (e.g., syringomyelia).

Equipment needed: For the acquisition of all SEPs, clinical electroencelography (EEG) recording equipment (e.g., scalp electrodes and recording amplifer) and stimulators are required. Needle electrodes can also be used in place of surface electrodes, and may save time during set-up. For most clinical applications (i.e., interpretation of peak amplitude and latency), a reduced number of recordings electrodes (n=2, an active and reference electrode) is appropriate. SSEPs, both mixed and dermatomal, require the use of an electrical stimulator. The stimulator should be capable of delivering a wide variety of pulse widths, frequencies and strengths of stimulation (0-40mA). CHEPs are recorded in response to rapid contact heat stimulation, typically delivered from a baseline temperature between 32-38^{o}C to a peak temperature of 54^{o}C (or adjusted to individual perception thresholds). LEPs use radiant heat stimulation to elicit EPs.

Costs: The cost of recording depends on the type of equipment ($20k to $80k). Currently, a commercially available CHEP stimulator is approximately $40k. For each patient, $10-$20 is needed for assessment (not including cost of examiners).

Algorithm for using SCI Electrodiagnostic Common Data Elements

Training: Medical training or supervision is required as for all clinical routine neurodiagnostics (e.g., nerve conduction studies, SSEPs, MEPs). If possible, a trained EEG technician would be appropriate to perform all SSEPs.

Protocol: All testing begins with properly cleaning (alcohol swabs) and lightly abrading the surface of the scalp where adhesive electrodes will be placed. In this regard, using needle electrodes will reduce the time for set-up. Electrodes should be positioned according to the 10-20 International electrode configuration. Peripheral and spinal electrodes should also be positioned accordingly. For SSEPs, the appropriate configuration of electrodes on the scalp will depend on the area of the body stimulated. Regardless of the stimulation site for CHEPs/LEPs, a vertex-recording electrode (referenced to link ears, A1-A2) can be used to acquire the most prominent waveform (i.e., N2P2). Where possible, a ground strap should be positioned between the site of stimulation and recording electrodes. For mixed nerve SSEPs, stimulation should be applied over the nerve of interest. To confirm placement, twitches of the appropriate muscle should be observed. If sensation is preserved, subject should report the distribution of stimulation. Stimulation intensity can be based on a threshold of motor or sensory stimulation (e.g., 1.5 motor or 4-5 x sensory detection threshold). To record dSSEPs, stimulation is performed on the cutaneous surface of specific dermatomes, within a peripheral boundary of a spinal segment (e.g., C6). By convention and for the purposes of comparison with light touch and pin prick findings, dSSEPs should follow dermatomes outlined by the International Standards for Neurological Classification of SCI. CHEPs and LEPs can only be used to stimulate peripheral cutaneous receptors, and thus the stimulation should always be placed over a specific dermatome of interest. Stimulation on the hairy skin will yield larger EPs than stimulation on glabrous skin. For SSEPs, averages of 200-500 stimulations at short inter-pulse intervals (3-4Hz) may be required to visually detect prominent cortical responses (e.g., N20, P40, etc.). In comparison, CHEPs and LEPs are delivered at long inter-pulse intervals (e.g., 8-12) and only require 10-20 stimulations. Increasing the baseline temperature of CHEPs has the effect of shortening the stimulation duration, and increasing the intensity of stimulation, improving the likelihood of observing cortical responses in areas with reduced sensation (Haefeli et al., 2013, Kramer et al., 2012, Kramer et al., 2013). During the acquisition of CHEPs, subjects should respond by rating perception to stimulation.

Duration of test: The length of testing is dependent on the number of areas stimulated and stimulation parameters (e.g., frequency). In general, set-up and testing of six sites (e.g., 2 mixed nerves and 4 dermatomes) should take approximately 1 hour.

Measurement and their psychometric properties: SEPs have generally demonstrated robust validity and reliability. However, due to high between subject variability in amplitude, latency of prominent waveforms is considered the most useful measure of conduction integrity. Longitudinal studies demonstrate little or no change in SSEPs during recovery from SCI, indicating the lack of spontaneous repair in the dorsal columns (Curt et al., 2008, Kramer et al., 2010, Spiess et al., 2012). However, as noted above, SEPs have been shown to be responsive to neurological deterioration. A dermatomal approach may be particularly sensitive to damage that is ascending in the spinal cord. Studies have examined the test-retest reliability of CHEPs

in healthy subjects (Kramer & Taylor et al., 2012, Ruscheweyh et al., 2013), but not in individuals with SCI.

Data analysis: Cortical waveforms are examined for peak latency (ms) and amplitude (μV). SSEPs should be corrected for differences in height. While normative values exist for SSEPs, a comparison with healthy control values should be made based on an individual laboratory basis. Normative CHEPs values (amplitude and latency) should be based on the stimulation site.

Data interpretation and pitfalls: If peripheral pathways are intact (i.e., normal nerve conduction studies), increased latencies of SSEPs reflect the severity of damage in the dorsal column. As a general guideline, clinically meaningful prolonged latencies of SSEPs should be greater than two times the standard deviation of healthy control values. Healthy control values should be established on an individual laboratory basis. At present, the clinical interpretation of CHEPs and LEPs are less clear than for SSEPs. Abolished waveforms coupled with no perception to contact heat stimulation should be considered indication of pathology in the spinothalamic tract. In cases where perception is reported but CHEPs are not observed, further assessment using the increased baseline temperature is warranted. Since CHEPs and LEPs require that the patient is alert and attending to stimulation, acquisition during the very acute phase of injury may be limited. Additionally, the most prominent CHEP and LEP waveform for clinical applications (i.e., vertex potential, N2P2) reflects a general response to afferent input (e.g., stimulation saliency). While there are some advantages of radiant heat stimulation over contact heat, LEPs require additional safety equipment (e.g., glasses for eye protection).

Relationship to other tests: Electrical perception threshold (EPT) can be performed in conjunction with SSEPs, oftentimes using the same stimulator (Kramer et al., 2008). Paired with MEPs, a thorough sensorimotor neurophysiological view of the spinal cord can be achieved. SSEPs and vibration thresholds have been previously examined and generally correspond (i.e., demonstrate similar deficits) (Hayes, 2002).

Clinical status: SSEPs are currently being widely used in clinical practice, across a variety of conditions. CHEPs and LEPs are at the beginning stages of clinical applications in SCI.

Classification: Supplemental

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Algorithm for using SCI Electrodiagnostic Common Data Elements

Test Name: Motor Evoked Potentials (MEPs)

Motor evoked potentials (MEPs) are muscular responses evoked by transcranial magnetic stimulation (TMS) of the motor cortex. MEPs may also be evoked by percutaneous electrical stimulation of the motor cortex[14]. This guideline describes the protocol and properties of the more widely used TMS evoked MEPs.

Purpose of Test: The MEP is a compound muscle action potential that usually has a tri-phasic waveform when measured with a bipolar EMG electrode configuration. The specific location of the stimulating coil on the scalp overlying the motor strip determines in which muscles an MEP will be recorded. Detection of an MEP confirms the anatomical contiguity of the cortico-spinal innervation to the targeted muscle and the amplitude and latency of the response provide indications of whether or not the central conduction is impaired. The derived measure of central motor conduction time (CMCT) further defines the conduction properties of the cortico-spinal tract. Additional insights into cortical and spinal (patho) physiology may also be derived from the short and long latency silent period ("cortical silent period") that follows the MEP in a contracting muscle[15]. The cortical silent period may also be recorded from contralateral muscles[16].

Level/Severity of spinal cord injury (SCI) : MEPs can be evoked inindividuals with motor incomplete injuries (ASIA C,D and E) and neurological level of injury (NLI) between C2-T12. In some cases of "discomplete" injury (ie functionally motor complete but anatomically incomplete) low amplitude MEPS may be recorded using techniques to *facilitate* the evoked response[4]. MEPs cannot be recorded from patients with cauda equina syndromes or more generally from patients with peripheral neuropathy.

When can the test be applied? Transcranial magnetic stimulation can be used in the acute stage, (including intra-operatively) in either tetraplegic or paraplegic individuals, provided the risk of seizure is low ie no significant brain injury and there are no pharmacological interventions, anesthetics or metal instrumentation that would confound the results. It can also be used in sub-acute or chronic states.

Equipment needed: The basic equipment is a transcranial magnetic stimulator plus standard electromyographic recording system. TMS can be applied with single pulse, dual pulse, or repetitive pulse stimulaton[17], and recordings made from a single muscle or multiple sites (polymyographic recording). Different applications eg EMG clinical laboratory versus intra-operative recording, require different instrumentation. An electrically "shielded" environment provides for better recording. A means to secure the stimulating electrode on the scalp is preferred. Additional precision and interpretation can be accomplished by using image (MRI) guided location of the stimulating electrode on the scalp in relation to the homuncular representation on the motor strip.

For multi-center clinical trials it is strongly advocated that the same stimulator, same stimulating coil (and direction of current), and recording conditions (amplifier bandwidth, filtering and signal processing) be used at each site (ie standardization across sites) to mitigate differences in recordings brought about by variation in the stimulation properties and EMG recording systems. It would also be prudent to have a standardized set of normative data and explicit criteria for

abnormality to aid interpretation of the outcomes, and/or a single expert involved in interpretation.

Costs: TMS stimulators and their different forms of stimulating electrodes vary from $5k-$25k depending on specifications and the types of recordings to be undertaken (see equipment needs above).

Training: Medical training or supervision is required; an experienced EMG technologist can acquire skills, in a week of supervised training, to elicit and record MEPs. Informed interpretation of the MEPs and their derived measures requires extensive knowledge of the relevant neurophysiology.

Protocol: Single-pulseTMS, of sufficient intensity, delivered to the appropriate location over the scalp, will normally induce a compound motor action potential (MEP) in many if not all muscles innervated by the cortico-spinal tracts that are activated. The presence of such responses confirms the structural integrity of the cortico-spinal tract; the MEP latency indicates whether nor not there are some conduction deficits contributing to any slowing of the response. Testing should be administered with patients resting quietly and relaxed in a standard posture[10] and in a non-distracting environment. Contraction of the targeted muscle, which may be possible in a motor incomplete patient, results in an increased amplitude of the evoked response. Other forms of facilitation, such as remote muscle contraction, or double stimuli, can be used to maximize detection of low amplitude responses[4]. There are different techniques available to measure the peripheral conduction time and these can be used to rule out peripheral conduction abnormalities contributing to delayed onset MEPs and to derive measures of central motor conduction time.

Duration of Test: A single TMS pulse delivered to the cortex only requires a few seconds to complete however most tests require multiple stimuli and averaging of responses and a full protocol duration would typically take from 30-90min.

Measurements and their psychometric properties: The primary measurements obtained include: 1) latency of the MEP, and 2)a measure of amplitude of the MEP (the peak-to-peak amplitude of the evoked tri-phasic or polyphasic wave) may be sufficient when central conduction is well preserved ; in the case of abnormal conduction such as would be expected following SCI then it may be necessary to provide full wave rectification of the signal and measurement of the area under the waveform (the time integral of the EMG voltage). By subtraction of peripheral motor conduction from the MEP latency it is possible to derive an estimate of 3) central motor conduction time (CMCT) thus :

CMCT(ms) = MEPlat - (Flat+Mlat - 1)/2

where F = F wave; M= M response; and -1ms is a constant for central turnaround time.

MEPs and CMCT measurements exhibit good reliability across trials and days and across both intra- and inter- rater assessments in able-bodied subjects; in SCI patients with impaired central conduction the results are more variable and warrant more repeated trials, averaging,

standardized recording conditions [10] and sometimes the use of facilitation techniques to ensure that low amplitude responses are detected as evidence of preserved innervation.

Data Analysis: MEP latencies include peripheral conduction times and care should be exercised to rule out abnormal peripheral conduction. MEP latencies and central motor conduction times are largely dependent on the physical stature of the individual (height) and adjustments for the height of the individual , length of cord or limb length may need to be considered. This has been done previously by plotting MEP latency as a function of height in control subjects, to establish linear regression models and confidence limits, and then identifying abnormal conduction times as those that are deviant to the normative data[11] . Standard descriptive and inferential statistics can be applied to the raw peak-to-peak amplitude measures or the area under the full wave rectified MEP waveform**.** Amplitude measures may be standardized relative to maximum amplitude M responses.

Data Interpretation: The risk of false negative interpretation of absent or very low amplitude response is high; where this is of significant interest eg in detecting subclinical benefits of a novel intervention it is prudent to employ facilitation techniques.

Relationship to other tests: The MEPS and central motor conduction times are the motor equivalents of SSEPS and central sensory conduction time in evaluating sensory conduction. ***Electrical*** stimulation of motor cortex can also be used to evoke MEPs and comparisons with magnetically evoked MEPS provide insight into cortical function. The recording of discrete, large amplitude, MEPS is usually associated with the preserved capacity for voluntary activation of motor units. The use of MEPs has been shown to be more sensitive than clinical assessment in the detection of preserved innervation in patients with SCI[9]. Associations with diffusion tensor imaging and fMRI have been reported[6, 7].

Clinical status: TMS is widely used clinically in the assessment of a number of neurological disorders involving the spinal cord (MS, myelopathies, congenital disorders etc) including SCI, both intra-operatively and in the clinic[2],[3] it also enjoys widespread use as a tool to sensitively detect any evidence of preserved innervation[13,14], better define the pathophysiology of SCI[1,6,]quantify central motor conduction deficits and sensitively detect the outcome of experimental interventions[8,11]. Useful references for identifying the changes in MEPs during recovery [18,19,20] and normative values are found below[21].

Classification: Supplemental

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Algorithm for using SCI Electrodiagnostic Common Data Elements

Test Name: Brain Motor Control Assessment (BMCA)

Purpose of Test: The BMCA examination quatitatively characterizes central nervous system control over spinal motor output. Through simultaneous multi-muscle surface EMG recording and the presentation of standardized reflex and volitional tasks, residual motor function within and caudal to a spinal cord lesion can be quantitatively assessed for arms, trunk and legs (Sherwood et al., 1996; McKay et al., 2012a). For those with clinically motor-complete SCI, the BMCA was used to develop the diagnosis of the discomplete syndrome (Dimitrijevic, 1988) in which neurophysiological evidence of translesional conduction is present (Sherwood et al., 1992; McKay et al., 2004). The BMCA has been used to assess spasticity (Dimitrijevic et al., 1980; Dimitrijevic and Sherwood., 1980; Priebe et al., 1996, Sherwood et al., 2000) and measure the effects of interventions to treat spasticity (Dimitrijevic et al., 1986; Priebe et al., 1997). Further, the surface EMG (sEMG) signals recorded during voluntary tasks are used to calculate similarity index values as a measure of the quality of the execution of those tasks, that is, the pattern of motor unit activity as measured in terms of magnitude and distribution across multiple muscles, relative to non-injured control subjects (Lee et al., 2004). Thus, the calculated similarity indices can provide a measure of any alteration in muscle coordination or dyssynergia induced by SCI.

Outcome Measures: Results objectively quantify standardized parameters of motor control which describe exogenous and endogenous input-output relationships in paralysis and the degree to which volitional control can select appropriate muscle(s) and initiate, maintain and terminate spinal motor output to those muscles, or indeed, to maintain those muscles in a quiescent state under modest input challenges. In conditions where voluntary motor activity is not requested, but reflexes are elicited, the ideal response may be no response; in requested voluntary maneuvers, however, individual responses are compared with those of neurologically intact individuals (Sherwood et al., 1996; McKay et al., 2012a).

Level/Severity of SCI: This method examines and characterizes/parameterizes motor control across the spectrum from paralyzed (Sherwood et al., 1992; McKay et al., 2004) to recovered motor function (McKay et al., 2011b). Protocols have been published and tested for use in examining motor control in arms, trunk and legs of people with SCI (Sherwood et al., 1996; Ovechkin et al., 2010; McKay et al., 2012a).

When can the test be applied? The BMCA protocol can and has been used in the acute stage, providing that the subject is medically stable, their limbs can be safely moved and they cognitively able to cooperate during the exam. The BMCA has also been used extensively in the sub-acute and chronic stages of recovery. Medications for pain and spasticity can diminish responsiveness and should be recorded for use during interpretation.

Where can the test be applied? This examination can be performed at the patient bedside or in the well-controlled environment of a neurophysiology lab.

Equipment needed: 8 to 32 channel EMG system with manually activated event marker and cuing tone generator. Data must be continuously collected, displayed and stored for all channels for the 30-60 minute duration of the recording. Analysis software is available for approximately

$5K. The original recordings were done on paper and manually analyzed (quantitation not available), but the computerized records are much more flexible and amenable to quantification.

Costs: Several systems on the market can provide the platform for performing this examination at a cost of between $30K and $40K, given a reasonable environment. The other cost concern is the time of two people, described below, currently needed to perform the roughly one-hour examinations of arms, trunk or legs, and the cost to analyze the results (expected to be nominal, and potentially exportable.)

Training: This examination currently requires 2 people. Ideally, the examiner is a physical or occupational therapist. An EEG/EMG technologist is the best choice for controlling data acquisition and processing to report. Both can be trained in a week to perform the examination and report the results.

Protocol: The protocol involves multiple sections. For all three body-regions mentioned, relaxation, reinforcement responses, volitional movement and reflex events in response to passive movements and to vibration, tendon taps and plantar stimulation are recorded. Motor evoked potentials (MEPs) may also be included in the protocol. (Sherwood et al, 1996).

Duration of Test: For maximum benefit, the entire protocol should be run, with an actual recording time of approximately 30-45 minutes. However, electrode application and removal adds a minimum of 15 – 30 additional minutes. Thus, approximately two hours' lab time should be scheduled for each test.

Measurements and their psychometric properties: Relaxation in the supine position allows the recognition of spasms and distonic continuous activation, either being evidence of abnormal motor control (Sherwood et al., 1996; McKay et al., 2011a; 2012b). The reflex sections and the voluntary sections are analyzed differently. Reflex measures generally assess responses that in neurologically intact subjects evoke little or no response; hence any response is a negative indicator, and the larger the response, the worse the indicator (McKay et al., 2004). Multi-muscle activation control patterns produced during voluntary movement are quantified using sEMG-based vector analysis that produced two values, total magnitude and a similarity index (SI) that relates the distribution of activity produced by a patient to that produced by neurologically intact control subjects (Lee et al., 2004). Face validitiy of this measure of voluntary control for SCI has been demonstrated relative to the ASIA Impairment Scale (Lim et al., 2004). Internal and test-retest reliability have also been demonstrated (Lee et al., 2004; Lim and Sherwood, 2005). Sensitivity to minimal volitional ability (McKay et al., 2004), lesion severity (Lim et al., 2005), change due to recovery (McKay et al., 2011b) and to corticospinal system conduction (McKay et al., 2005) has also been published. Finally, sensitivity has also been demonstrated in relation to clinical function including gait speed (Lim et al., 2005), respiratory function (Ovechkin et al., 2010), functional independence (Ovechkin et al., 2013).

Data Analysis: Prior to analysis, data reduction is performed. The base data is comprised of the full bandwidth surface EMG recordings from each examined muscle (typically 8 – 32 muscles), which is converted to an envelope representing the amount of activity from each muscle during standard time windows based on event marks in the recording. This allows

visualization and quantitation of the distribution of activity over the muscles in response to the challenge maneuvers. BMCA standards include three repeated trials for motor tasks from which the per-muscle amplitudes are averaged to provide values to measure discomplete markers (McKay et al., 2004). The calculation of similarity index values that quantify multi-muscle distribution of motor unit activity has recently been automated in a software package (Lee et al., 2004)(BioCat software, Valencia, CA).

Data Interpretation: On the basis of spinal motor output in the form of motor units fired, the BMCA quantitatively describes the ability of the central nervous system to select appropriate motor units (multi-muscle distribution), activate those motor units, inhibit antagonistic and distant units and terminate their activation. All parameters of motor control examined are interpreted in relationship to the values acquired by performing the examination in neurologically intact control groups. Each segment of the protocol provides relevant information. Any motor unit activity recorded during relaxation can be considered to be episodic spasms unless identified as voluntary movement attempts, or dystonic continuous activity persisting after repeated instruction to relax. Both are indicative of inappropriate CNS motor control. Responses in lower limbs to supralesional reinforcement tasks (Valsalva, Jendrassik, neck flexion, shoulder shrug) are also not seen in neurologically intact subjects. Voluntary movement attempts are measured and tracked using the previously described index calculations. Passive stretch is again evaluated by the amount of sEMG activity recorded. Withdrawal presence and suppression quantify the degree to which volitional control of inhibitory function has been preserved. Non-injured subjects are able to varying degrees to volitionally suppress this cutaneomuscular reflex.

Relationship to other tests: Systematic comparisons of these tests have not been made, other than comparison to spasticity scores (Sherwood et al., 1997), because no quantitative tests evaluating voluntary control quality have been identified. However, the SI scores do correlate with clinical measures (Lim et al., 2004; Ovechkin et al., 2013)

Clinical status: These tests have been used to monitor patients as they recover from SCI (McKay et al, 2011b) or when undergoing procedures to modify altered motor control (Priebe et al., 1997). Further, initial efforts to identify prognostic markers have been made with some potentially useful findings (McKay et al., 2011b). From the published studies referenced in this document it can be said that the earlier after injury one with a SCI can produce motor unit activation on command, the more likely will be their recovery of volitional movements. However, broad use in the clinical environment has not been achieved but is the goal of current efforts.

Classification: Exploratory

Algorithm for using SCI Electrodiagnostic Common Data Elements

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Algorithm for using SCI Electrodiagnostic Common Data Elements

Test Name: Sympathetic Skin Responses (SSRs), also known as the Electrodermal Response

Purpose of Test: To provide an indication of intact connections from the brain to autonomic sympathetic outflow from the thoraco-lumbar levels of the spinal cord. The test may compensate for the lack of autonomic testing in the current International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) as specified by the American Spinal Injury Association (ASIA).

Level/Severity of spinal cord injury (SCI): The SSR can be used in patients with any degree of injury (AIS A-E) and neurological level of injury (NLI) between C2-S3. It has specific application for determining levels of injury in the thoracic spinal cord and may supplement the ISNCSCI sensory tests of LT and PP.

When can the test be applied? SSR can be used in the acute stage of spinal cord injury provided the type of stimulation used to elicit the SSR is compatible with the condition of the patient (e.g. inspiratory gasp might be inappropriate). It can be used in the sub-acute and chronic states of SCI.

Equipment needed: (1) any standard electrophysiological recording amplifier and data capture system. (2) An electrical stimulator capable of delivering repetitive square wave pulses with either manual or computer control of timing. (3) Surface skin stimulation/recording electrodes.

Costs: Electrophysiological amplifiers and A/D data capture may already be available linked to other tests (e.g. motor evoked potentials, somatosensory evoked potentials, clinical electrophysiology). Cost for a suitable stand alone system (amplifier plus data acquisition) would be ~$10k. Suitable electrical stimulators cost from $5k (manual control).

Training: An experienced EMG/EEG operator could acquire skills to elicit and record SSRs following a week of instruction and training. Informed interpretation of the SSRs requires knowledge of the relevant autonomic neurophysiology.

Protocol: Subjects should be lying comfortably on a bed in a quiet, warm (ideally 24±0.5°C) room throughout an SSR test. This protocol is followed as temperature is known to affect conduction velocity of unmyelinated sympathetic fibres[1] and distribution of the SSR over the body surface[2]. Any arousal stimulus can be used to elicit a SSR. Conveniently, electrical stimulation of a peripheral nerve may be used. Single pulse (width 0.5 ms) stimulation at an intensity 1.5 times the motor threshold of the stimulated nerve, most commonly the median nerve at the wrist and the peroneal nerve at the ankle, are usually employed. In subjects with complete SCI who do not present a response to nerve stimulation, the stimulation intensity should be progressively increased until a SSR occurs, (up to 4-5 times the motor threshold of normal subjects). In tetraplegic subjects, with a level of lesion higher than the roots of origin of the median nerve, the supra-orbital nerve may be stimulated. As an alternative to electrical nerve stimulation, a sudden, brief acoustic stimulus may be used, or the subject requested to make a voluntary gasp. Supra-pubic tapping is known to elicit the SSR but may be contra-indicated if episodes of autonomic dysreflexia are anticipated. A minimum of 4 trials should be

performed for each stimulus. Habituation of the SSR is a feature of the SSR in many people and the intervals between stimuli (several seconds) should be randomized to minimise anticipation. It may be useful to repeat stimulation up to ten times to reveal habituation[3] and to gradually increase the strength of stimulation during a trial[4].

The SSR is most readily recorded from the palm of the hand or sole of the foot. Self-adhesive electrodes are applied to the palm and dorsum of the hand, (sole and dorsum of the foot). A ground electrode may be fixed to any remote site. The amplifier should have a gain of x100 and band width filters typically set at -3bB below 0.1 Hz and above 100 Hz. The SSR recording trace may be set from 0.5 s before to 8 s after the trigger stimulus to allow for the long latency and duration of the response (seconds).

Duration of Test: A palmar and plantar SSR test on both sides of the body takes approximately 30-45 min to perform.

Measurements and their psychometric properties: The principal measure is the presence or absence of the SSR at one or more of four locations (right and left, palmar and plantar). Further measures are the amplitude and latency. A normal SSR generally has a biphasic form with an initial negative excursion (palm/sole negative with respect to dorsal surface) followed by a positive excursion with peak to peak amplitudes of between 0.5-1.3 mV (hand) and 0.1-1 mV (foot). Duration of the SSR is generally around 4s. Normal latencies are ~1.5s (hand) and ~2s (foot).

Anxiety and anticipation of repeat tests may generate electrodermal activity that can distort a stimulus provoked response. Habituation affects the amplitude and form of the SSR leaving the latency constant[5].

Additional Data Analysis: None required.

Data Interpretation: Abnormality in the autonomic sympathetic pathway is evident if one or more SSRs from the four recording sites (left & right, hand & foot) are absent, unless the lack of response can be attributed to interruption by the spinal lesion of the afferent input pathway to the brain. The SSR may be regarded as abnormal if amplitudes between the left and right side differ by at least 50%[6]. A consensus as to what aspects of the SSR may be considered abnormal is yet to be reached.

Further interpretation of SSR tests should consider the following points. The central pathways mediating the SSR are not well understood but are thought to involve the brain stem, hypothalamus and several areas of the cerebral cortices[7]. Descending tracts of supraspinal origin innervate preganglionic cholinergic neurons in the intermedio-lateral cell columns. The axons of those neurons exit via ventral root and white rami to synapse in the paravertebral sympathetic ganglia. The postganglionic axons from neurons in the paravertebral ganglia then synapse on eccrine sweat glands in the skin via muscarinic receptors. The paravertebral sympathetic ganglia are supplied by spinal segments T1 to L2 but it appears that descending access to and output from T4 to T6 is required for palmar SSRs and T9 – T10 for plantar SSRs[6, 8, 9]. Accepting this distribution, there have been a number of studies using the SSR that could be

interpreted as showing incomplete spinal injury with respect to the sympathetic autonomic nervous system in otherwise AIS A graded patients[6, 10-14].

In general, peripheral nerve stimulation below a complete SCI lesion does not elicit an SSR[10, 11, 15], suggesting that the spinal cord isolated from supraspinal circuits does not support the SSR. The exception appears to be that a SSR may be provoked by pudendal nerve stimulation[15]. This may in itself provide a useful test of the integrity of spinal sudomotor effector circuits below the level of spinal injury.

Relationship to other tests: Cardiovascular responses to tilt table tests of autonomic function are well predicted by preservation of SSRs[12]. Proclivity to autonomic dysreflexia is indicated by absence of SSRs[16]. Sweat production is correlated positively with the second (positive) component of the SSR[17].

Clinical status: SSR has been used widely in psychiatric studies to signal emotional changes and is the basis of the well-known lie detector test. The SSR has been available for around 20 years as a non-invasive bed-side test to reveal abnormal functioning of the autonomic nervous system due to central nervous system dysfunction[18].

Evaluation: SSR provides an indication of the spinal level at which sympathetic outflow from the spinal cord to the paravertebral ganglionic chain is intact. Further tests would be required to assess autonomic function relating to systems other than sweat production.

Classification: Supplemental

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