Pathophysiology of knee jerk reflex abnormalities in L5 root injury

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Summary

Although the knee jerk reflex is mediated by the L3 and L4 nerve roots, evidence exists that altered knee jerk expression may occur with exclusively L5 radiculopathy. The present study set out to identify the factors responsible for knee jerk reflex abnormalities in L5 monoradiculopathy. We analyzed clinical and electrophysiological data in 56 subjects affected by L5 monoradiculopathy. Seventeen patients (30.3%) showed an abnormal knee reflex. L5 patients with an abnormal knee reflex differed significantly, in severity of pretibial muscle damage, from those with a normal knee reflex. On the basis of evidence, in humans, of a specific spinal pathway linking the pretibial and quadriceps muscles, we infer that an impairment of the proprioceptive drive from the pretibial muscles to spinal premotor excitatory interneurons contacting quadriceps motor neurons is the main causative factor responsible for reducing knee jerk expression. This mechanism should be considered to avoid misinterpretation of knee jerk reflex changes in lumbar radiculopathies.

KEY WORDS: basic neuroscience, neurosurgery, spinal cord and root disorders

Introduction

The testing of deep tendon reflexes is an essential diagnostic tool for determining neurological disturbances in neuromuscular disorders and it is applicable for the detection of level-specific nerve root involvement in patients with lumbar radiculopathy. Striking the patellar tendon with a reflex hammer stretches the muscle spindle in the quadriceps femoris muscle; this produces a signal that synapses directly onto an alpha-motor neuron at the level of L3 or L4 in the spinal cord. From there, the motor neuron conducts an efferent impulse back to the quadriceps femoris, triggering contraction. An abnormal knee jerk reflex may thus predict L3/L4 root injury in patients with no disease apart from lumbar radiculopathy. A recent paper evaluating the accuracy of physical examination for detecting chronic lumbar radiculopathy reported altered knee jerk reflex expression in radiculopathies other than L3 and L4 (Iversen et al., 2013). Furthermore, in a selected cohort of patients affected by L5 monoradiculopathy due to a herniated disc, a number of subjects presented with an absent or reduced knee jerk reflex in the absence of any clinical or instrumental L3/L4 root involvement (Mondelli et al., 2013a,b). The aforementioned observations oblige us to consider other causative factors of knee jerk reflex abnormalities.

The aim of this study was to analyze putative factors responsible for altered knee jerk reflex expression in patients with selective L5 radiculopathy. To this end, we reviewed the data from two previous studies by our group that were conducted to explore clinical and electrophysiological findings in patients with L5 monoradiculopathy (Mondelli et al., 2013a,b).

Materials and methods

In the previous prospective studies, we reported magnetic resonance imaging (MRI) findings and clinical and electrophysiological results in 108 consecutive patients affected by lumbosacral monoradiculopathy due to a herniated disc (Mondelli et al., 2013a,b). The diagnosis of radiculopathy was made on the basis of history (acute pain appearing 1-12 months before the enrollment period), pain at the dermatome of L4, L5 or S1, with or without low back pain, and MRI evidence of a herniated disc compressing the root corresponding to the painful dermatome. Exclusion criteria were: age >65 years, diabetes, rheumatic diseases, malignancy in the previous five years, polyneuropathy, radiculopathy in a different area or resulting from causes other than herniated disc (tumors, osteophytes, facet hypertrophy), lumbosacral spine surgery,

MRI signs of lumbar canal stenosis, spondylolysis, and/or spondylolisthesis.

All MRI studies were reviewed by the same expert neuroradiologist, who excluded all cases in which more than one root was affected (Mondelli et al., 2013a). In view of the aim of the present study, only data (drawn from the original database) referring to patients affected by L5 monoradiculopathy were considered and analyzed.

The following aspects were reviewed: demographic data, body mass index (BMI), nerve conduction study and electromyography (EMG) findings from nerves and muscles related to the L5 root, knee jerk tendon reflex, ankle tendon reflex, hypoesthesia in the dermatome with radicular pain (as shown by at least one of: impaired touch, pinprick and two-point discrimination sensitivity), paraesthesia in the dermatome with radicular pain, L5 myotomal strength, and visual analog scale (VAS) rating of pain. Subjects with both L5 monoradiculopathy and abnormalities of the quadriceps muscle were excluded from the analysis.

The selection of the muscles and nerves analyzed was based on a human experimental study that examined segmental sensory and motor innervation of the lumbosacral spinal nerves (Liguori et al., 1992). The electrophysiological methods used are reported in detail elsewhere (Mondelli et al., 2013a). Briefly, for this study we considered the antidromic sensory conduction velocity and sensory nerve action potential (SNAP) amplitude of the superficial peroneal nerve, the motor conduction velocity and compound muscle action potential (CMAP) amplitude of the deep peroneal nerve, and the EMG findings of five muscles (adductor magnus, quadriceps femoris, tibial anterior, peroneus longus, gastrocnemius). Lowerlimb skin temperature was kept constant above 32°C with an infrared lamp. EMG included observation of abnormal spontaneous activity at rest (positive sharp waves, fibrillations and high-frequency repetitive discharge), qualitative evaluation of motor unit action potentials and quantitative evaluation of recruitment at maximum effort in the tibialis anterior and peroneus longus muscles. The EMG of a muscle was considered abnormal when denervation activity at rest in at least two separate areas of the investigated muscle and/or decreased recruitment at maximum effort (fewer motor unit action potentials firing at higher rate) were recorded (Fisher et al., 1978).

A single neurophysiologist, who was blinded to MRI results, performed all the physical and electrophysiological examinations. The cases were definitively included in the study when the level of root compression due to disc herniation, as identified by the neuroradiologist, corresponded to the clinical level hypothesized by the neurophysiologist.

Statistical analysis

Regularized logistic regression was applied to assess the relationship between the dependent dichotomous variable “knee reflex” (1=abnormal, 0=normal) and the explanatory variables investigated in the sample. The set of explanatory variables consisted of: abnormal SNAP amplitude of the superficial peroneal nerve (that is the SNAP amplitude of the affected leg) and the difference between the superficial peroneal nerve SNAP amplitudes recorded in the affected and the unaffected leg (continuous variables), VAS pain scale rating (continuous variable), strength loss (1=yes, 0=no), paraesthesia (1=yes, 0=no), sensitivity loss (1=yes, 0=no), and EMG alteration of the L5 muscles (tibialis anterior and peroneus longus muscles) (1=yes, 0=no). In order to exclude potential sources of collinearity from the multivariate logistic model, the following variables that had shown significant correlations were discarded: normal SNAP amplitude of the superficial peroneal nerve, EMG alteration of the L5 muscle, at least one sensitivity alteration, strength deficit. The regression model was constructed for the purpose of hypothesis generation. In this setting, we were interested in determining the independent predictors of an event (i.e., the abnormal knee reflex outcome).

However, in general, models resulting from the use of automated variable selection methods are likely to contain spurious variables that have mistakenly been identified as predictors of the outcome. To reduce this risk, we needed to independently validate the model in a separate dataset. By adopting a regularized logistic regression model where convex penalties are included, we tackled the major issues related to the automated variable selection. Actually, logistic regression models with quadratic penalization are expected to correctly detect the significant predictors along with their interaction structures; they are therefore fit for handling correlated discrete factors with a binary response.

The variables were selected with the elastic net method (implemented by the “glmnet” algorithm) which is a hybrid of ridge regression and lasso regularization (Zou and Hastie, 2005). Elastic net regularization involves two levels of model restrictions, and even though it introduces bias into the estimation, it reduces predictor error variance. But this possible extra bias is a minor concern, because our main purpose was to identify the significant variables rather than to determine the predictive accuracy. It is also known that regularization is not inclined to overfitting, however, in order to assess the robustness of the elastic net model, we applied the leave-one-out cross-validation (LOOCV) procedure. LOOCV allowed us to test the model in a dataset (validation set) separate from the datasets (training sets) adopted for estimating the parameters.

The results of the model obtained in the training sets were averaged. For each significant variable we tabulated the estimated coefficient (beta), the standard error, the estimated odds ratio (as given by the exponential of beta), the lower and upper bounds of the 95% confidence interval, the Wald statistic and the corresponding p-value. Model accuracy was assessed by measuring the area under the receiver operating characteristic (AUC) curve. The percentiles of the distribution of the knee reflex normal outcomes within the sample formed the range of the cut-off values from

which the best threshold was determined. The statistical difference between the AUC curve and the area under the chance line (that equals 0.5) was evaluated through the z-test. The goodness of fit for the logistic regression was also assessed by means of the likelihood ratio (LR) test. All the statistical tests were two-tailed and 0.05 was taken as the level of significance. Statistical analysis was performed with MATLAB software (The MathWorks, Inc., Natick (MA), USA), version 7.5.

We used a non-parametric test (Mann-Whitney U test) to evaluate differences between demographic data, BMI and duration of symptoms between the two groups.

Results

Of the 58 patients (33 males and 23 females) affected by L5 monoradiculopathy, two were excluded because of the presence of EMG alterations in the quadriceps muscle. Forty-nine (87.5%) disc herniations were at L4-L5 level, five (8.9%) at L5-S1 level and two (3.6%) at L3-L4 level (migrated disc). The most frequent zone of radicular compression was in the lateral recess due to "paramedian" disc herniation (64.3% of cases). The disc herniation was "foraminal" in the remaining cases (35.7%). Of the 56 patients, 17 (30.3%, 9 males and 8 females) had an absent (two subjects) or reduced (15 subjects) knee tendon reflex compared with the contralateral side. The knee reflex of the unaffected leg could be elicited normally in all 56 patients. Of the subjects with knee reflex abnormalities, only one had a reduced ankle tendon reflex. The mean age of the patients (17 subjects) with absent or reduced knee reflex was 47.6±9.7 years, whereas in the other group (39 subjects) it was 51±8.9 years (difference not significant); in the former group the BMI was 25.4±3.2 kg/m^2, in the latter 24.9±3.7 (difference not significant). The mean duration of symptoms was 3.9±2.6 and 4.2±2.8 months, respectively (difference not significant).

Table I shows the electrophysiological and clinical results in the two groups of patients. The EMG was more frequently abnormal in subjects with an absent or reduced knee reflex than in the other group: 64.7% (11/17 patients) vs 20.5% (8/39 patients). All 11 patients in the former group had EMG anomalies in both the explored L5 muscles (peroneus longus and tibialis anterior).

The multivariate analysis showed that in all the training sets the probability of a knee reflex abnormality was significantly determined by the presence of the EMG anomalies in L5 muscles in addition to a constant term (some statistical results are shown in Table II).

The EMG assessment variable entered the model with a positive coefficient equal to 1.2667 (±0.0615), therefore the presence of an EMG alteration corresponds to a higher probability (almost 3.5 times) of observing an abnormal knee reflex. The LR test (LR=7.14; p=0.0075) indicated that the full model (i.e., the one containing the intercept and the EMG assessment variable) performed better than the one obtained under the null hypothesis (intercept as minimal size required for accuracy). The average value of the AUC curve was 0.7778 (±0.0917) (z=3.0297; p=0.0012), which corresponds to a medium level of accuracy of the model. The sensitivity of the model was 64.71%,

Table I - Mean electrophysiological values (±SD) and clinical features of L5 monoradiculopathy patients with normal and abnormal knee reflexes.

	SCV SP affected leg	SCV SP unaffected leg	SNAP SP affected leg	SNAP SP unaffected leg	CMAP DP affected leg	MCV DP affected leg	VAS score	Hypoesthesia (% pts)	Paresthesia (% pts)	Muscle strength deficit (% pts)	EMG abnormalities (% pts)
Normal (n. 39)	46.9±4.2	46.9±3.3	17±9.2	17.4±1	4.54±2.2	46.58±3.8	51.3±21	47%	64%	53%	8 (20.5%)
Abnormal (n. 17)	45.6±6	47.4±4	11.7±5.8	14±5.4	5.22±2	46.6±3.1	64±18.6	65%	82%	61%	11 (64.7%)

EMG abnormalities refers to the tibialis anterior and peroneus longus muscles. Hypoesthesia and paresthesia refer to the dermatome with radicular pain. Muscle strength refers to L5 myotomes.

Abbreviations: CMAP=compound muscle action potential amplitude; DP=deep peroneal nerve; MCV=motor conduction velocity; n.=number of subjects; pts=patients; SP=superficial peroneal nerve; SCV=sensory conduction velocity; SNAP=sensory nerve action potential amplitude; Normal=normal knee reflex; Abnormal=abnormal knee reflex.

Table II - Results of the regularized logistic regression.

Variable	beta	s.e. beta	exp(beta)	95%CI lower	95%CI upper	Wald statistic	p-value
Intercept	-1.7342	0.0481	0.1765	-1.8308	-1.6377	-36.0166	0
S.P. SNAP	-0.0381	0.0673	0.9625	-0.1732	0.0969	-0.5662	0.5712
VAS score	0.0172	0.0673	1.0173	-0.1178	0.1523	0.2560	0.7979
EMG abnormalities	1.2667	0.0615	3.5494	1.14343	1.3901	20.5899	0

Abbreviations: CI=confidence interval; SP=superficial peroneal nerve; SNAP=sensory nerve action potential amplitude; VAS=visual analog scale

the specificity 52.63%, the positive predictive value 37.93%, the negative predictive value 76.92%, and the odds ratio 2.0370. Their corresponding 95% confidence intervals were, respectively: [41.99% - 87.41%], [36.75% - 68.51%], [20.26% - 55.59%], [60.73% - 93.12%] and [0.6252 - 6.6364].

Discussion

Thirty-three percent of our patients with L5 monoradiculopathy had an abnormal knee reflex; by contrast, ankle tendon reflex abnormality was an exceptional event in these subjects (Mondelli et al., 2013a,b). Since the knee jerk reflex reduction in our patients is not due to L3/L4 root injury, other causative factors need to be considered. On the basis of experimental results from animal and human studies, it is proposed that a critical impairment of the afferent input originating from pretibial muscles is the main factor responsible for depressing the excitability of knee motor neurons (MNs) in patients with L5 radiculopathy. Spinal interneuron pathways are an elaborate system of motor control. The simplistic idea that the spinal cord functions as a relay system for descending and afferent commands has been replaced by the concept of a dynamic system able to regulate and produce purposeful movements rather than stereotyped segmental reflex responses (McCrea, 2001). In fact, spinal interneuron pathways controlling lower limb MNs are strategically positioned to assist bipedal stance and gait. These pathways have been shown to affect the excitability of the MNs innervating homonymous muscles acting at the same joint as well as those innervating heteronymous muscles acting at different joints. Studies on the implications of such pathways in human spasticity have documented that alterations in these interneuronal pathways modify muscle synergies (Marque et al., 2001; Maupas et al., 2004; Masakado et al., 2005; Dyer et al., 2009)

On the other hand, input from peripheral afferent systems contributes significantly to spinal reflex circuits, together with muscle synergies during posture or locomotion. For example, research performed in animals and humans has identified specific afferent systems, such as group I and II muscle afferents conveying pretibial proprioception, that control MNs innervating the quadriceps muscle (Forget et al., 1989a,b; Meunier et al., 1990). In particular, discharge of spindle afferent fibers originating from pretibial muscles and running in the common peroneal nerve evokes non-monosynaptic facilitation in the quadriceps MNs (see also Marque et al., 2001; Maupas et al., 2004). This functional link between pretibial muscles and quadriceps MNs is potentially implicated in the knee jerk reflex depression observed in L5 monoradiculopathy patients. Indeed, a critical impairment of pretibial group I and II drive to premotor interneurons projecting to quadriceps MNs could make these MNs less responsive to the homonymous monosynaptic Ia discharge. This mechanism could ultimately reduce the knee jerk expression.

This interpretation is supported by the following results of our study: i) the statistical analysis showed that pretibial muscle motor damage (electrophysiologically documented) was the only factor significantly associated with a high likelihood (almost 3.5 times) of observing depression of the knee jerk reflex in L5 monoradiculopathy patients; ii) the above statistical result, together with the absence of a correlation between knee jerk depression and sensory changes (pain, paresthesia, sensitivity loss), leads us to conclude that the L5 motor root damage was the main causative factor of the knee jerk reflex abnormalities in our patients. Indeed, in addition to alpha motor axons, L5 ventral root compression may involve gamma motor axons innervating pretibial muscle spindles from which group Ia and II afferent fibers originate, thus reducing their excitatory effect on quadriceps MNs; finally, iii) the preservation of the soleus jerk reflex observed in our patients is consistent with the absence of excitatory proprioceptive pathways from pretibial to extensor ankle muscles (Pierrot-Deseilligny and Burke, 2012); in fact, being antagonist muscles, these are linked by reciprocal and mutual inhibition.

We therefore conclude that the most likely possible mechanism able to account for depression of the knee jerk reflex in L5 monoradiculopathy is impairment of the proprioceptive drive from pretibial muscles to spinal excitatory interneurons contacting quadriceps MNs.

Lumbar radiculopathy is a common reason for physician consultations and imaging referrals. Clinical examination, and in particular the test for tendon reflexes, aims to clarify whether there is mechanical impingement of a nerve root (Cannon et al., 2007). The observations reported in the present paper suggest that knee jerk reflex impairment cannot be used to disprove a clinical suspicion of L5 monoradiculopathy.

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