Neurogenic calf amyotrophy with CK elevation by entrapment radiculopathy; Clinical, radiological, and pathological analyses of 18 cases

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Abstract

Objective: To characterize the clinical, radiological, and pathological manifestations of 18 cases showing neurogenic calf amyotrophy with creatine kinase (CK) elevation by entrapment radiculopathy (NCACKEER).

Methods: We retrospectively reviewed and evaluated the medical records of patients who complained of weakness or atrophy of the calf muscles in our department between 2004 and 2019. We identified 18 cases fulfilling the proposed criteria of NCACKEER. We extracted neurological, laboratory, neurophysiological, and neuroradiological data from all cases. Moreover, we evaluated biopsy specimens from the gastrocnemius in 4 cases.

Results: Eighteen NCACKEER cases exhibited the characteristic findings that can discriminate previously known myopathies or polyneuropathies affecting distal legs. We noticed male predominance (72%) with an average age at diagnosis of 65.6 years. Muscle weakness or atrophy was localized in the distal legs, with Achilles tendon reflexes absent in all cases. We observed elevated serum CK levels with a range from 237 to 2294 IU/L. All electromyography (EMG) studies showed neurogenic changes in the affected muscles. Lumbar spinal MRI exhibited either spinal canal stenosis at various vertebral levels or intervertebral foraminal stenosis at L4/5 and L5/S1 in all cases with significant straightening spinal and sacral alignments. All muscle biopsy specimens showed findings of neurogenic muscular degeneration with no inflammatory

infiltrations. Cases with higher CK elevation had more necrotic muscle fibers.

Conclusion: We established the clinical characteristics of NCACKEER. Evaluations of serum CK level and skeletal muscle CT imaging are useful for screening, and lumbar spinal MRI, EMG and/or muscle biopsy are necessary for diagnostic confirmation.

Introduction

Lumbosacral radiculopathy frequently causes calf amyotrophy; however, co-occurrence of muscle swelling or serum creatine kinase (CK) elevation is rare. Neurogenic muscle swelling due to S1 radiculopathy, and occasionally L5 has been previously described.[2-8, 10-12, 14-20, 22-25, 27, 28] A previous report also presented a similar case of calf amyotrophy with serum CK elevation due to S1 radiculopathy with no muscle swelling.[21] Nonetheless, pathogenesis and clinical features of these disorders remain unclarified.

Herein, we retrospectively studied a large series of 18 cases with neurogenic calf amyotrophy with CK elevation by entrapment radiculopathy (NCACKEER) confirmed by newly developed diagnostic criteria from the Japanese single center. We analyzed clinical, radiological, and pathological manifestations of NCACKEER cases and notably 15 did not show visible muscle swelling. NCACKEER is a distinctive disease entity that can be discriminated from distal myopathies or polyneuropathies.

Methods

We retrospectively studied the electronic medical records of patients who visited the department of neurology in Gunma university hospital between January 2004 and October 2019. Patients were included as having NCACKEER if they presented the following features: (1) two or more consecutive confirmation of high serum CK levels above the reference value at intervals of one month or more, (2) unilateral or bilateral calf muscle degeneration demonstrated by CT or MRI images, and (3) L5 or S1 spinal nerve root compression due to vertebral degenerative lesions demonstrated by lumbar spinal MRI. We excluded patients with obvious myopathy or polyneuropathy causing calf amyotrophy. In addition, patients with overexercise-, muscle crush-, or drug-induced serum CK elevation were excluded by repeated serum CK evaluations and discontinuation of the suspected drugs. We additionally examined cases with calf muscle degeneration due to L5 or S1 radiculopathy without serum CK elevation under similar conditions. We collected lumbar spinal MRI images of amyotrophic lateral sclerosis (ALS) patients with minimal degenerative lumbar changes as control data for statistical comparison to analyze the spinal and sacral sagittal MRI parameter details of NCACKEER cases

Clinical, laboratory, neurophysiological, and neuroradiological data

We retrospectively reviewed and collected clinical, laboratory,

neurophysiological, and neuroradiological data from the medical records. Clinical data included demographics, medical history, neurological findings such as presence of calf swelling, muscle weakness or atrophy, sensory disturbance, tendon reflexes, ability of standing on toes, and others. We defined disease duration as the period from the onset of symptoms to the point of taking a skeletal muscle CT. Laboratory data included a range of serum CK levels (minimum to maximum), electromyography (EMG) findings in lower legs, nerve conduction study (NCS) of the tibial nerve motor conduction velocity (MCV), and pathological findings of muscle biopsy from gastrocnemius (GC) or tibialis anterior (TA) muscles. Neuroimaging data were collected from a skeletal muscle CT or MRI and a lumbar spinal MRI. We evaluated in the sagittal view the presence or absence of spinal canal stenosis (SCS) based on the lumbar spinal MRI findings, and intervertebral foraminal stenosis (IFS) at L4/5 and L5/S1 in the axial view. We measured the spinal sagittal parameters of the lumbar lordosis angle (LL) at L1-S1 and the pelvic parameters of the sacral slope angle (SS) using the supine lumbar spinal MRI according to the procedures described previously: we defined LL as the angle formed by the straight lines at the level of the upper endplate of L1 and S1, and SS was defined as the angle formed by the straight line at the level of the upper endplate of S1 and the horizontal plane analyzed on the mid-sagittal MRI image.[29]

Muscle pathology assessments

We performed open muscle biopsy on the GC or TA muscle with the use of local anesthesia. We then rapidly froze the biopsied tissue specimens, sectioned horizontally at 10 μm thickness, and stained them with hematoxylin-eosin (HE), modified Gomori trichrome, and beta-nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-TR) stainings. We evaluated the muscle biopsy specimens of five NCACKEER patients on the following pathological findings: grouped atrophy, target/targetoid fibers, necrotic fibers, regenerating fibers, central nuclei, hypertrophic fibers, fiber splitting, inflammatory infiltrations, and increased fat and connective tissues. Moreover, three certified neurologists independently reviewed the pathological findings of each case (M.S., H.K., and Y.F.), while, in cases of disagreement the respective grading was decided after discussion.

Statistical analysis

We performed all statistical analyses with the SPSS ver. 25.0 software (IBM Japan, Tokyo, Japan). A propensity score matching (PSM) analysis was used to minimize selection bias and to balance significant differences in age at examination and sex between the NCACKEER and control groups. We used Student's t-test to compare LL and SS between the NCACKEER and control groups. *P*-values less than 0.05 were considered statistically significant. Respective values are expressed by mean, range, standard deviation, and percentage of patients.

Results

We identified 18 NCACKEER fulfilling the inclusion criteria. Additionally, we found one case with calf muscle degeneration due to L5 or S1 radiculopathy without serum CK elevation. We also enrolled 18 ALS patients who were equally aged and sex-matched as a control group to compare the spinal sagittal MRI parameters.

We conducted muscle biopsy on 5 NCACKEER cases; 4 cases from the GC muscle and 1 case from the TA muscle. Figure 1 summarizes a combined picture of the skeletal muscle CT, lumbar spinal MRI, and HE staining of biopsied specimens in each NCACKEER patient. Similarly, online supplementary figure 1 summarizes a combined picture except for the muscle biopsy of the other 13 NCACKEER patients.

Representative presentation of NCACKEER Case 3

Case 3 was a 39-year-old Japanese man who began to feel difficulty for walking and could not stand on his right toe. At age 41, he frequently felt muscle cramps in his right calf, and an orthopedist suspected lumbar disc herniation. At age 43, his serum CK was found to be elevated at 701 IU/L, and he was admitted to our department for suspected focal myositis. His height, body weight, and body mass index (BMI) were 179 cm, 101 kg and 31.5 kg/m^2, respectively. His thigh and calf circumferences (right/left) were 48.0/46.0 cm and 41.0/39.5 cm, respectively. His calves

were not swollen, and he had no sensory disturbance in the lower limbs. He could not stand on his toes; however, he could walk independently with no assistance. His patellar tendon reflexes (PTR) reacted normally while the right Achilles tendon reflex (ATR) was absent. EMG showed obvious neurogenic changes in motor unit potentials (MUPs) with high amplitudes and prolonged durations, and reduced interferences of MUPs in his left GC muscle. A skeletal muscle MRI showed hyperintensities in the right calf muscles on T2-weighted and short tau inversion recovery images (T2WI and STIR, respectively). A right GC muscle biopsy revealed neurogenic muscular changes of grouped atrophy, fiber-type grouping, and target/targetoid fibers without inflammatory infiltrations (Figure 1 and Table 1). Case 3 also showed necrotic fibers, regenerating fibers, central nuclei, hypertrophic fibers, and fiber splitting as additional findings. His serum CK levels were subsequently elevated reaching up to 1004 IU/L. At age 47, a skeletal muscle CT revealed moderate atrophy of bilateral GC and soleus muscles, and mild atrophy of bilateral extensor hallucis longus (EHL), extensor digitorum longus (EDL), semitendinosus, and biceps femoris muscles. Lumbar spinal MRI confirmed SCS in the sagittal T2WI view and both L4/5 and L5/S1 IFS in the axial T2WI view (Figure 1), finally diagnosing NCACKEER.

Clinical and laboratory characteristics of NCACKEER

We summarize the clinical and laboratory characteristics of 18 NCACKEER

cases in Table 2 and Table e-1. The average age at diagnosis [mean (SD)] was 65.6 (7.6) years, and 13 patients were male. (72%) The average BMI [mean (SD)] was 25.1 (3.5) kg/m^2. Only 3 cases exhibited unilateral calf swelling (17%), while 2 of them showed transient swelling (Cases 4 and 18). Eight out of 18 cases (44%) showed some sensory disturbance in their lower limbs with 3 cases pertaining to the bilateral S1 dermatome (Cases 5, 13, and 14) and 5 cases to the bilateral L5-S1 dermatomes (Cases 2, 9, 10, 11, and 12). Eight out of 18 cases had muscle cramps in their calves (44%). The ATRs of all cases were bilaterally absent or at least regarding the severely affected side. Fourteen cases (78%) showed dissociated reactivity between PTRs and ATRs, namely loss of ATR with preserved PTR. Fifteen out of 17 cases (88%) could not stand on their toes. All cases could walk unassisted.

The average levels of minimum and maximum serum CK [mean (SD)] were 321.7 (228.9) and 947.6 (598.0) IU/L, respectively. The tibial nerve NCSs were evaluated in 15 cases. Only Case 5 showed a reduced tibial nerve MCV of 33.5 m/sec, suspected to be due to alcohol abuse. The remaining 15 cases showed tibial nerve MCVs faster than 40 m/sec. We evaluated EMGs in 15 cases while all cases exhibited neurogenic changes in MUPs with high amplitudes and prolonged durations, and reduced interferences of MUPs in their affected TA or GC muscles (Figure 2). Only Case 8 showed complex repetitive discharges in the right soleus muscle. Mutational analysis of the dysferlin gene was negative in Case 4.

Neuroimaging characteristics of NCACKEER

The skeletal muscle CT showed the findings of muscular degeneration and atrophy of GC and soleus muscles in all NCACKEER cases, and mild atrophy of EHL and EDL muscles were also observed (Figure 1 and online supplementary figure 1). The TA muscle frequently degenerated (Cases 7 and 8) in Figure 1, and Cases 2, 4, 11, and 14 in online supplementary figure 1). In addition to lower leg muscles, thigh flexors such as biceps femoris, semitendinosus, and semimembranosus muscles, which were innervated by S1 nerve root, were degenerated to a certain degree. Chronological gradual progression of muscular degeneration in calf muscles, lower leg extensor muscles, and thigh flexor muscles was confirmed by the skeletal muscle CT in Case 7 (Figure 3A). The skeletal muscle MRI T2WI and STIR images of Case 5 showed hyperintensities at the corresponding area that was degenerated on CT image (Figure 3B). The skeletal muscle MRI T2WI of case 18 showed a transient right calf swelling that was spontaneously improved within 2 months with no treatments (Figure 3C). Serum CK level of Case 18 was elevated to 1067 IU/L at the time muscle swelling appeared, and two months later, it was still comparably high to 1198 IU/L even though the muscle swelling improved.

Lumbar spinal MRI showed the findings indicative of L5 and/or S1 nerve root compression in all NCACKEER cases which was supported by the findings of SCS or

L5/S1 IFS, respectively (Figure 1 and online supplementary figure 1). Even in cases in which SCS was unremarkable at the sagittal views, L5/S1 IFS at the axial views was confirmed (Case 6 in Figure 1). There were no findings of spinal cord compression that could cause epiconus syndrome on spinal MRI in all 18 cases.[26]

Figure 3D showed an additional case of a 60-year-old Japanese male with normal serum CK who was considered to have similar pathogenesis to NCACKEER. The skeletal muscle CT showed right predominant degeneration of bilateral calves and biceps femoris muscles. Lumbar spinal MRI showed mild lumbar SCS and L4/5 IFS. EMG confirmed the neurogenic changes in his right GC muscle.

Significant lumbar straightening in NCACKEER

Baseline demographics including age at MRI and gender were well balanced between NCACKEER and control groups (online supplementary table 1). There was a significant difference in the average of LL and SS [mean angle (SD)] between NCACKEER and control groups [29.1° (9.8) vs. 44.8° (9.1), $p < 0.001$, and 32.2° (7.2) vs. 39.0° (7.8), $p = 0.002$, respectively] (Table 3 and online supplementary table 1).

Pathological features of muscle biopsy of NCACKEER

Table 1 summarized the pathological features of 5 NCACKEER cases who undergone muscle biopsy. The average levels of serum maximum CK [mean (SD)] were

1230.5 (226.5) and 339.7 (95.0) in male and female patients, respectively. Cases 3 and 7 showing highly elevated CK tended to have more necrotic and regenerating fibers than cases with mildly elevated CK (Cases 6, 8, and 15). Inflammatory infiltrations were not observed in all cases. Figure 4 showed histopathological findings of the representative NCACKEER cases with higher CK elevation (Case 7). Case 7 had obvious neurogenic degenerative changes such as grouped atrophy of muscle fibers (Figures 4A) and target/targetoid fibers. (Figures 4B) Case 7 with higher CK elevation tended to have more necrotic fibers (Figure 4C, arrow) and regenerating fibers (Figure 4D, arrow) than cases with milder CK elevation. Case 7 also showed central nuclei (Figure 4E, arrow), hypertrophic fibers, and fiber splitting (Figure 4F, arrow).

A case with surgical intervention (Case 10)

Case 10 (Figure 3E) was a 59-year-old Japanese man when he was diagnosed as having probable NCACKEER. His serum CK initially showed 80-144 IU/L at age 54, but was gradually elevated to 461-475 IU/L at age 55 when numbness and pain in bilateral lower legs and difficulty in standing on toes appeared. The skeletal muscle CT showed muscle atrophy in bilateral calf muscles. Lumbar spinal MRI showed SCS and IFS at L4/5 and L5/S1. He underwent multiple lumbar fenestrations for SCS at L3/4 and L4/5, which resulted in mild improvement of numbness and pain, although serum CK remained similarly high level. After additional lumbar fenestration at L2/3, the

compression and redundancy of cauda equina were released, then serum CK levels were mildly decreased to 230-258 IU/L although the lumbar IFS unchanged. There was no significant progression of motor symptoms thereafter, but numbness and pain remained.

Proposed diagnostic criteria of NCACKEER

We proposed the new diagnostic criteria of NCACKEER based on the results of clinical, laboratory, neuroradiological, and pathological analyses of our 18 cases (Table 4). These criteria consist of (A) Laboratory features, (B) Imaging features, and (C) Clinical features. We classified diagnosis possibility into 3 categories: definite, probable, and possible. The "definite" category requires characteristic laboratory, imaging, and clinical features as well as muscle biopsy confirmation of neurogenic findings with necrotic fibers. The "probable" category requires characteristic laboratory, imaging, and clinical features but a lack of muscle biopsy. The "possible" category requires characteristic laboratory and imaging features but a lack of muscle biopsy, EMG assessment, and clinical features. We applied these criteria to all 18 cases, and diagnosed 4 cases as definite (Cases 3, 6, 7, and 8), 10 cases as probable (Cases 2, 5, 9, 10, and 13-18), and 4 cases as possible (Cases 1, 4, 11, and 12) categories of NCACKEER (Table 2).

Discussion

This study investigated 18 cases of NCACKEER with or without calf muscle swelling, and clarified its clinical, laboratory, neuroimaging, and pathological characteristics. This study also revealed two important clinical observations found in NCACKEER cases. First, lumbosacral radiculopathy could cause neurogenic calf amyotrophy with serum CK elevation without muscle swelling. Second, MRI evaluation on the findings of SCS and IFS were both important, and spinal and sacral sagittal parameters as for spinal and sacral straightening were useful tool for diagnosing NCACKEER.

Almost all previous reports on cases with calf amyotrophy due to lumbosacral radiculopathy were associated with calf muscle swelling.[2-8, 10-12, 14-20, 22-25, 27, 28] Costa *et al.* systematically reviewed the literature on these cases with muscle swelling published in 1966 to 2005, and summarized their clinical characteristics as follows: S1 radiculopathy (86%), cramps (47%), weakness (67%), absent Achilles tendon reflex (97%), high serum CK (74%), and EMG denervation (86%).[5] These features were similar to our cases except for higher frequency of muscle swelling found in the previous reports. A previous study examined the muscle pathology of 7 cases with calf muscle swelling associated with lumbosacral radiculopathy.[23] It suggested that calf enlargement was due to muscle fiber hypertrophy and atrophy combined with increased volume of connective tissues, which were similar to our biopsied cases. As discussed so far, our NCACKEER cases without muscle swelling would be considered

to belong to the same spectrum as previously reported cases with muscle swelling because of the consistency of clinical and pathological findings.

The reasons why NCACKEER frequently affects the calf muscles and causes serum CK elevation are controversial. The strength of calf muscles should be strong enough to support the entire body weight while standing or walking. When radiculopathy causes calf muscle atrophy, the workload on the remaining innervated muscles will increase. This hypothesis has been suggested in the previous reports of similar cases with visible muscle swelling.[2, 19] Since our cases exhibited relatively higher BMI (mean 25.1 kg/m^2), increased weight load on the calf muscles was likely to cause NCACKEER. Clinical and myopathological findings of our NCACKEER cases suggested the potential remodeling mechanism of calf muscles, in which muscle fiber hypertrophy cannot compensate weakness, and subsequent muscle fiber splitting or necrosis will result in serum CK elevation.

To the best of our knowledge, this study represented a largest series of lumbar spinal MRI details of NCACKEER cases. All 18 cases except for Case 6 had clear findings of SCS at various vertebral levels so that S1 nerve root entrapment could cause NCACKEER. In cases with unremarkable SCS (i.e., Case 6), it is important to evaluate IFS on the axial view. In general, L4 nerve root passes through the L4/5 intervertebral foramen, and L5 nerve root passes through the L5/S1 intervertebral foramen. Although the calf muscle is mainly innervated by S1-S2 nerve root, it is reported that anomalous

innervations of the calf muscle by L5 nerve root could be observed.[30] Therefore, the L5/S1 IFS may cause atrophy of the calf muscles.

In the present study, there were many cases in which both SCS and IFS coexisted, therefore, we need to discuss which degenerative changes can cause NCACKEER. Case 10 who underwent orthopedic surgery showed a reduced level of hyperCKemia after releasing of SCS, indicating the pathology of NCACKEER was more profoundly related to SCS than IFS. Since the number of surgical cases was small, we should accumulate the knowledge from similar cases.

Moreover, higher frequency of spinal and sacral straightening was found in NCACKEER cases, because angular parameters of LL and SS were significantly decreased. Previous studies demonstrated the association between LL, SS, and lumbar disc degenerative diseases.[29] As the spine and sacrum straightened, the gravity axis moves forward, and compressive force of gravity increases, it results in exacerbation of the disc degeneration and lumbosacral radiculopathy.[29] LL is the index originally developed using standing X-ray; however, reports showed that LL could be calculated by lumbar spinal MRI at supine position.[1] According to the MRI analysis, NCACKEER cases showed significantly smaller LL and SS angles than control subjects indicating significant spinal and sacral straightening as a skeletal feature of NCACKEER. These spinal and sacral sagittal parameters might be useful in differentiating NCACKEER from other disorders.

On the other hand, referring to a large cohort study of Japanese degenerative spinal disease, the MRI findings of moderate or severe lumbar SCS were present in 76.5% of people with mean age of 66.3 years.[13] Therefore, over-diagnosis of NCACKEER should be avoided, and it is necessary to carefully exclude non-specific serum CK elevation associated with prescription drugs, overexercise, and muscle crush. In this study, all suspected prescription drugs that could potentially cause serum CK elevation were discontinued in all cases. In addition, the proposed diagnostic criteria of NCACKEER required confirmation of continuous serum CK elevation at intervals of more than one month. Besides, the all four cases with definite NCACKEER who underwent GC muscle biopsy showed neurogenic changes with necrotic fibers pathologically, indicating that the elevated serum CK was not a non-specific finding but a result of muscle fiber necrosis. A previous report postulated the mechanism of hyperCKemia in a similar case to NCACKEER was muscle fiber necrosis and regeneration due to prolonged denervation and re-innervation.[21] Muscle biopsy from GC muscles is a useful test to exclude both non-specific serum CK elevation and inflammatory infiltrations.

It is important to make a differential diagnosis of NCACKEER from distal myopathies such as Miyoshi myopathy or GNE myopathy especially in cases who did not show sensory disturbance in clinical practice. A needle EMG is very useful because observation of neurogenic changes can exclude a possibility of distal myopathies for the

purpose of initial screening. GC muscle biopsy would be required to examine whether neurogenic muscular degeneration exist to obtain a definite diagnosis of NCACKEER. It is also important to evaluate whether S1-innervated dorsal thigh muscles as well as GC and soleus muscles are affected.

The so called “benign calf amyotrophy” in the previous literatures would be an alternative pathological condition similar to NCACKEER.[9] Except for the presence of lumbosacral radiculopathy found in NCACKEER, clinical characteristics were similar to our cases in the points of male predominance, elderly onset, fewer association of muscle swelling, and neurogenic muscular changes confirmed by EMG and muscle biopsy. NCACKEER and benign calf amyotrophy may have the same pathogenesis; however, we had clarified all lumbosacral radiculopathy evidence of confirmed by SCS and IFS on MRI, L5- or S1-innervated muscle atrophy, and S1-dermatome sensory deficit. Following evaluation of SCS on sagittal MRI images cannot tell the presence of compressive radiculopathy, an IFS finding on axial MRI images is necessary to diagnose NCACKEER.

There are several limitations in this study. First, since the presence of nerve root compression was retrospectively evaluated based on clinical and conventional lumbar spinal MRI findings, we could not fully assess the nerve root compression using MR neurography or other methods. Second, the number of muscle biopsy cases was rather small to examine the relationship between the levels of serum CK elevation and

severity of muscle histopathology regarding muscle pathology. It is necessary to examine additional biopsied cases and investigate the mechanism of serum CK elevation. Third, a potential selection bias could exist due to our center being a university hospital. Our 18 NCACKEER cases were all mildly affected, and their activities of daily living were not severely interfered. It is possible that much milder NCACKEER cases would exist in the community hospitals, and NCACKEER might be more common than we expected. Because neurological deficits at an early stage of NCACKEER are very mild, NCACKEER might exist among cases with idiopathic asymptomatic hyperCKemia. To identify NCACKEER cases effectively, a task of standing on toes or skeletal muscle CT examination would be useful for screening, because weakness of calf muscles is an initial symptom of NCACKEER.

Conclusion

In conclusion, we clarified the wide spectrum of the clinical, laboratory, neuroimaging, and pathological features of NCACKEER, and proposed new diagnostic criteria. Evaluation of dissociated reactivity between PTRs and ATRs, standing on toes, serum CK levels, and muscle CT assessment are useful for screening. In addition, lumbar spinal MRI, needle EMG and/or muscle biopsy are necessary to confirm the findings of neurogenic calf amyotrophy, and make a diagnosis of NCACKEER.

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Conflicts of interest

The authors report no disclosures.

Data availability statement

Anonymized data can be made available by request to qualified investigators.

Author contributions

MS and YI contributed to the conception and design of this study. MS, HK and YF reviewed the muscle pathology. HK, KM, MI, KN, YF and YI contributed to the interpretation and critical revision of the manuscript.

Standard protocol approvals and ethical issues

The ethical committee of research on human subjects at the Gunma University Graduate School of Medicine approved the protocol of this study (HS2019-210).

Patient consent for publication

Written consent was obtained from Case 3 and the case presented in Figure 3D.

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Table 1

Pathological evaluation of muscle biopsy specimens of 5 NCACKEER cases

Case #	Specimen	Age	Sex	CKmax (IU/L)	Grouped atrophy	Target fibers	Necrotic fibers	Regenerating fibers	Central nuclei	Hypertrophic fibers	Fiber splitting	Inflammatory infiltrations	Increased FCT
3	**GC**	**47**	**M**	**1004**	+	+	+	+	+	+	+	−	−
6	**GC**	**70**	**F**	**237**	+	−	+	−	+	+	+	−	+
7	**GC**	**73**	**M**	**1457**	+	+	+	+	+	+	+	−	−
8	**GC**	**71**	**F**	**466**	+	+	+	−	+	+	+	−	+
15	**TA**	**61**	**F**	**316**	+	+	−	−	+	+	−	−	+

Abbreviations: **CK** = creatine kinase; max = maximum; **FCT** = fat and connective tissues; **GC** = gastrocnemius; **TA** = tibialis anterior; **M** = male; **F** = female

Table 2

Clinical, laboratory, and neurophysiological characteristics of 18 NCACKEER cases

Case #	Age	Sex	Duration (years)	BMI (kg/m^2)	CC	Calf swelling	LL SD	MC	PTR (R / L)	ATR (R / L)	Standing on toes	CKmin (IU/L)	CKmax (IU/L)	Tibial N MCV (m/s)	EMG (lower limb)	Muscle biopsy	Diagnostic category
1	**78**	**M**	**24.0**	**23.5**	**H-CK**	**−**	**−**	**+**	**+ / +**	**− / −**	**possible**	**280**	**1046**	**41.8**	**neurogenic**	**NE**	**possible**
2	**69**	**M**	**15.7**	**27.4**	**Gait D**	**−**	**+**	**+**	**+ / +**	**− / −**	**impossible**	**325**	**579**	**NE**	**neurogenic**	**NE**	**probable**
3	**47**	**M**	**13.8**	**31.5**	**Gait D**	**−**	**−**	**+**	**+ / +**	**− / +**	**impossible**	**296**	**1004**	**46.0**	**neurogenic**	**Rt. GC**	**definite**
4	**64**	**M**	**11.0**	**29.3**	**Calf swelling**	**+ (Lt)**	**−**	**+**	**+ / +**	**+ / −**	**impossible**	**71**	**1630**	**46.3**	**NE**	**NE**	**possible**
5	**62**	**M**	**10.3**	**22.9**	**MC, LLSD**	**−**	**+**	**+**	**+ / +**	**− / −**	**impossible**	**597**	**1699**	**33.5**	**neurogenic**	**NE**	**probable**
6	**70**	**F**	**9.3**	**23.9**	**Gait D, LLSD**	**+ (Lt)**	**−**	**−**	**− / −**	**− / −**	**impossible**	**186**	**237**	**42.0**	**neurogenic**	**Rt. GC**	**definite**
7	**73**	**M**	**7.9**	**26.7**	**Gait D**	**−**	**−**	**+**	**+ / +**	**− / −**	**impossible**	**719**	**1457**	**47.0**	**neurogenic**	**Rt. GC**	**definite**
8	**71**	**F**	**5.7**	**20.7**	**Gait D**	**−**	**−**	**−**	**− / −**	**− / −**	**impossible**	**36**	**466**	**46.5**	**neurogenic**	**Lt. GC**	**definite**
9	**66**	**F**	**4.7**	**22.4**	**Gait D**	**−**	**+**	**−**	**+ / +**	**− / −**	**impossible**	**121**	**201**	**52.6**	**neurogenic**	**NE**	**probable**
10	**59**	**M**	**4.5**	**21.8**	**Gait D, LLSD**	**−**	**+**	**−**	**− / −**	**− / −**	**impossible**	**80**	**475**	**43.0**	**neurogenic**	**NE**	**probable**
11	**68**	**M**	**4.4**	**26.0**	**Gait D**	**−**	**+**	**+**	**+ / +**	**− / −**	**possible**	**403**	**722**	**40.3**	**NE**	**NE**	**possible**
12	**76**	**M**	**4.3**	**22.5**	**H-CK**	**−**	**+**	**−**	**+ / +**	**− / −**	**NE**	**207**	**709**	**45.1**	**NE**	**NE**	**possible**
13	**68**	**M**	**4.1**	**26.2**	**Gait D, LLSD**	**−**	**+**	**−**	**+ / +**	**− / −**	**impossible**	**106**	**321**	**47.4**	**neurogenic**	**NE**	**probable**
14	**53**	**F**	**3.8**	**30.9**	**Gait D**	**−**	**+**	**−**	**+ / +**	**− / −**	**impossible**	**278**	**915**	**NE**	**neurogenic**	**NE**	**probable**
15	**61**	**F**	**2.2**	**27.8**	**Gait D**	**−**	**−**	**−**	**− / −**	**− / −**	**impossible**	**159**	**316**	**NE**	**neurogenic**	**Lt. TA**	**probable**
16	**68**	**M**	**1.1**	**22.4**	**MC, H-CK**	**−**	**−**	**+**	**+ / +**	**− / −**	**impossible**	**557**	**2294**	**48.4**	**neurogenic**	**NE**	**probable**
17	**59**	**M**	**0.8**	**18.8**	**H-CK**	**−**	**−**	**−**	**+ / +**	**− / −**	**impossible**	**812**	**1787**	**42.9**	**neurogenic**	**NE**	**probable**
18	**69**	**M**	**0.2**	**27.7**	**Gait D**	**+ (Rt)**	**−**	**−**	**+ / +**	**− / −**	**impossible**	**557**	**1198**	**40.9**	**neurogenic**	**NE**	**probable**

Abbreviations: **BMI =** body mass index; **CC** = Chief complaint; **LLSD =** lower limb sensory disturbance; **MC =** muscle cramp; **PTR =** patellar tendon reflex; **ATR** = Achilles tendon reflex; **CK** = creatine kinase; **min** = minimum; **max** = maximum; **Tibial N** = Tibial nerve; **MCV** = motor conduction velocity; **EMG** =

electromyography; **M** = male; **F** = female; **H-CK** = hyperCKemia; **Gait D** = gait disturbance; **NE** = not examined; **GC** = gastrocnemius; **TA** = tibialis anterior

Table 3

Summary of clinical and demographic characteristics of 18 NCACKEER cases

Patient Characteristics (n = 18)	
Male, n (%)	**13/18 (72)**
Age at diagnosis, y, mean (SD) (minimum-maximum)	**65.6 (7.6) (47-78)**
Time from diagnosis, y, mean (SD) (minimum-maximum)	**7.1 (5.9) (0.17-24.0)**
BMI, kg/m^2, mean (SD)	**25.1 (3.5)**
Calf swelling, n (%)	**3/18 (17)**
Sensory disturbance, n (%)	**8/18 (44)**
Muscle cramp, n (%)	**8/18 (44)**
Loss of ATR in the affected limbs, n (%)	**18/18 (100)**
Dissociated reactivity between PTR and ATR (loss of ATR with preserved PTR), n (%)	**14/18 (78)**
Inability of standing on toes, n (%)	**15/17 (88)**
CK min, IU/L, mean (SD) (minimum-maximum)	**321.7 (228.9) (36-597)**
CK max, IU/L, mean (SD) (minimum-maximum)	**947.6 (598.0) (237-2294)**
Neurogenic changes in EMG, n, (%)	**15/15 (100)**
Neurogenic changes in muscle biopsy, n, (%)	**5/5 (100)**
Lumbar lordosis angle, mean (SD)	**29.1 (9.8)**
Sacral slope angle, mean (SD)	**32.2 (7.2)**

Abbreviations: **BMI** = body mass index; **ATR** = Achilles tendon reflex; **PTR** = patellar tendon reflex; **CK** = creatine kinase; **EMG** = electromyography

Table 4

Diagnostic criteria for neurogenic calf amyotrophy with CK elevation by entrapment radiculopathy (NCACKEER)

Characteristic features

A. Laboratory features

1. Two or more consecutive high serum creatine kinase levels above the normal upper limit at intervals of one month or more are confirmed to exclude serum creatine kinase elevation associated with overexercise, drugs, or muscle crush.
2. Electromyography (EMG) confirms neurogenic findings indicative of reinnervation in lower legs (i.e. polyphasic, high amplitude, prolonged duration motor unit potentials, and reduced interference pattern). Fibrillation potentials, positive sharp waves, and complex repetitive discharges may also exist.
3. Neurogenic and additional changes of muscle biopsy specimen from gastrocnemius muscle.
   a. Biopsy specimen from gastrocnemius muscle (innervated by S1-S2, occasionally L5) confirms neurogenic findings such as grouped atrophy, fiber type grouping, and target/targetoid fibers with necrotic fibers.
   b. Biopsy specimen from gastrocnemius muscle may show regenerating fibers, central nuclei, hypertrophic fibers, fiber splitting, and increased fat and connective tissues in addition to neurogenic changes.
   c. Biopsy specimen from gastrocnemius muscle shows no inflammatory infiltrations.

B. Imaging features

1. Skeletal muscle CT or MRI shows unilateral or bilateral calf muscle degeneration.
2. Lumbar spinal MRI confirms L5 or S1 nerve root compression supported by spinal canal stenosis on sagittal view and/or intervertebral foraminal stenosis of the affected side on axial view. Note that asymptomatic spinal canal stenosis is common in the elderly.
3. Lumbar spinal MRI on sagittal view may show straightening of the lower spine and sacrum supported by a decreased angle of the lumbar lordosis (L1-S1) or the sacral slope.

C. Clinical features

1. Inability of standing on toes or to repeat flexion and extension of ankle on standing more than 5 consecutive times.
2. Achilles tendon reflexes (ATRs) in the affected limbs are typically reduced or absent, and dissociated reactivity between patellar tendon reflexes (PTRs) and ATRs, namely loss of ATR with preserved PTR may be present.
3. Lower limb sensory disturbance is typically unremarkable but may exist.
4. Frequent muscle cramps in the lower legs may exist.
5. Males are predominantly affected than females.
6. Patients with higher body mass index are predominantly affected.
7. Elderly people are predominantly affected than younger people.
8. Swelling of the lower leg may exist.
9. Functional prognosis is typically favorable, and only a subset of patients may use wheelchairs. Disease progression may stop in a subset of patients.

Diagnostic categories

Definite NCACKEER

- Characteristic laboratory features of A1 and A2, imaging features of B1 and B2, and clinical features of C1 and C2 with muscle biopsy confirmation of A3a and/or A3b and A3c.

Probable NCACKEER

- Characteristic laboratory features of A1 and A2, imaging features of B1 and B2, and clinical features of C1 and C2, but a lack of muscle biopsy (A3).

Possible NCACKEER

- Characteristic laboratory feature of A1, and imaging features of B1 and B2, but a lack of muscle biopsy (A3), EMG assessment (A2), and clinical features (C1 and C2).

Figure Legends

Figure 1.

Skeletal muscle CT, lumbar spinal MRI, and muscle histopathology findings of 5 NCACKEER cases

Skeletal muscle CT images at the levels of middle thighs (upper row) and calves (middle row), lumbar spinal T2-weighted images at mid-sagittal (lower left column) and axial (lower right column) views at the levels of L4/5 and L5/S1 intervertebral foramina, as well as muscle histopathology in hematoxylin and eosin (HE) staining (lowest right) of 5 NCACKEER cases were shown with the same arrangement of items (Cases 3, 6, 7, 8, and 15 that shared the same case number in Table 1., Scale bar = 100 μm). All cases exhibited calf amyotrophy on CT images, and neurogenic muscular degeneration in HE staining. Axial MRI images showed L4/5 and/or L5/S1 intervertebral foraminal stenosis with or without various degrees of spinal canal stenosis in all cases. Sagittal MRI images showed spinal straightening in all cases to a certain degree.

Figure 2.

Representative EMG findings of a NCACKEER Case 17

Representative EMG findings of a NCACKEER Case 17 (Table 1 and online supplementary figure 1) examined at the tibialis anterior (TA, left column) and the medial head of gastrocnemius (GC, right column) muscles were shown. EMG recordings of both muscles revealed remarkable neurogenic changes with prolonged durations, high amplitudes, and polyphasic motor unit potentials (upper rows), and a decreased interference pattern (lower rows). The interference pattern was more severely reduced in GC than in TA muscles. There was no abnormal spontaneous activity at rest in both TA and GC muscles.

Figure 3.

Neuroimaging characteristic details of 5 cases

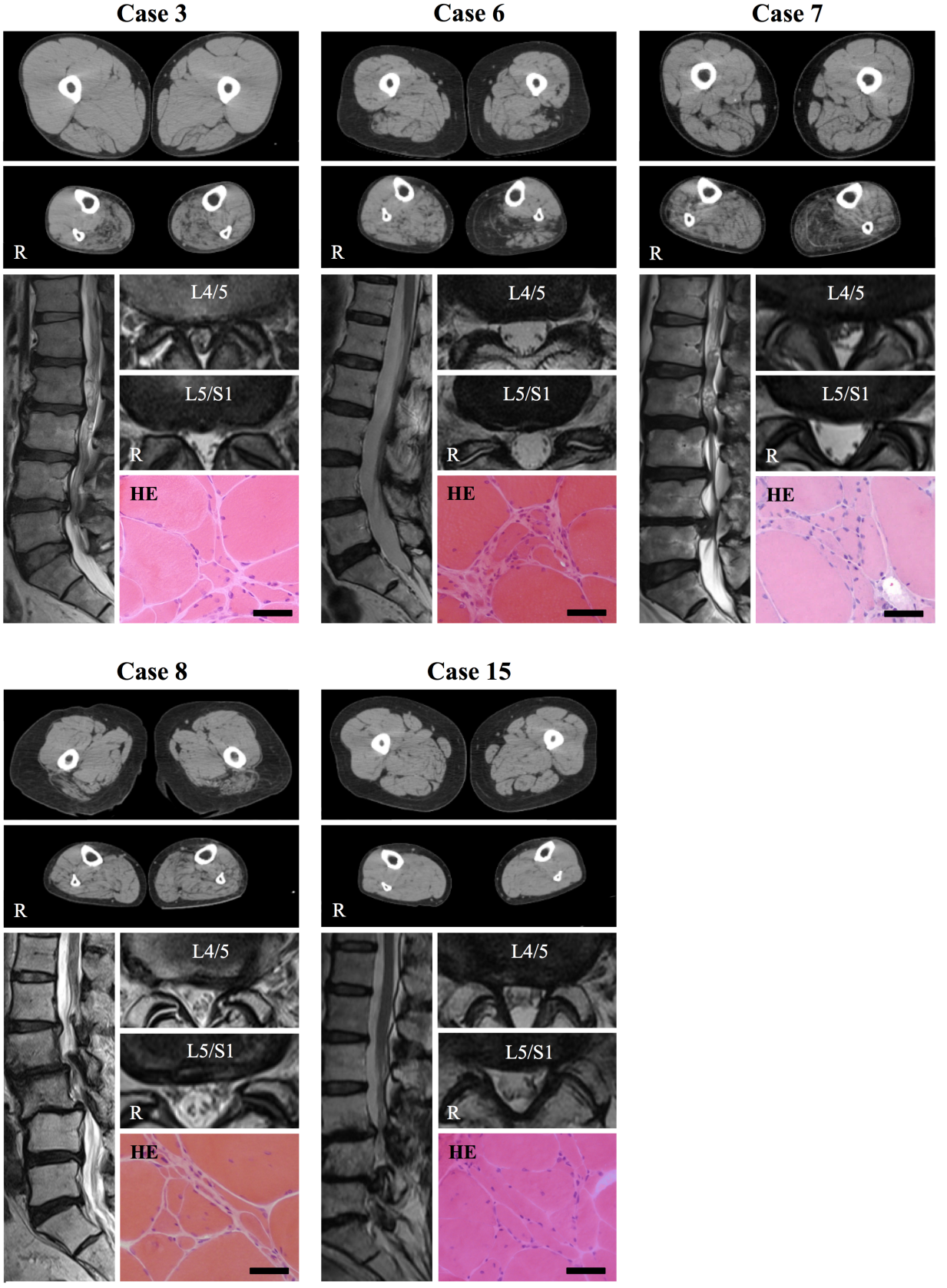
(3A) Chronological changes of the skeletal muscle CT findings in Case 7 showed progressing left predominant calf amyotrophy. The skeletal muscle CT was repeated every 2 years, and followed until 6 years from onset. Degeneration of the lower leg extensor muscles and thigh flexor muscles such as semimembranosus muscles were also mildly progressed. (3B) Comparisons of radiological findings of the skeletal muscle CT and those of MRI at thigh (left column) and calf (right column) levels in Case 5 were shown. Muscle CT (upper row) exhibited mild atrophy of left calf, and T2-weighted images (T2WI, middle row) and short tau inversion recovery (STIR, lower row) exhibited high intensities at the corresponding area that appeared degenerated on CT. In addition, right semimembranosus muscle and right tibialis anterior muscle where muscle atrophy was not evident by CT exhibited high intensities on T2WI/STIR. (3C) Chronological changes of the calf muscle swelling on MRI images in Case 18 were shown. The skeletal muscle MRI T2WI showed a transient right calf swelling that was improved spontaneously within 2 months without any treatments. (3D) The skeletal muscle CT and lumbar spinal MRI images of a 60-year-old man with normal serum creatine kinase (CK) were shown. He complained of difficulty for standing on right tiptoe and some gait disturbance. The skeletal muscle CT showed right predominant degeneration of bilateral biceps femoris (upper row) and calf (middle row) muscles. Lumbar spinal MRI showed L4/5 intervertebral foraminal stenosis (lower right column). His maximum serum CK level was 168 IU/L. EMG confirmed the neurogenic changes in right gastrocnemius muscle. Nerve conduction study was normal. (3E) The skeletal muscle CT, preoperative and postoperative lumbar spinal MRI (T2WI), and serum CK level changes in Case 10 were shown. The skeletal muscle CT showed bilateral calf muscle amyotrophy. Preoperative lumbar MRI showed spinal canal stenosis at the L2/3, L3/4, and L4/5 levels on sagittal view,

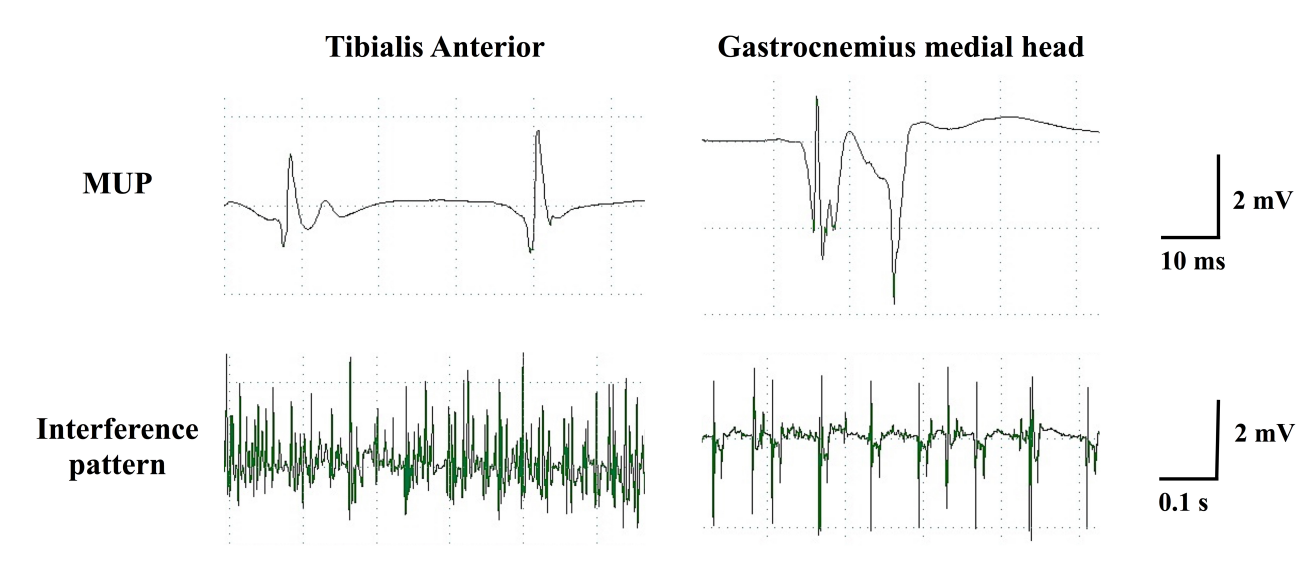
and lumbar intervertebral foraminal stenosis at the L4/5 and L5/S1 levels on axial view. Preoperative CK levels ranged from 461-475 IU/L. This case underwent surgery of lumbar fenestration at the L2/3, L3/4, and L4/5 levels. Postoperative lumbar MRI showed that the compression and redundancy of cauda equina were released, but the lumbar intervertebral foraminal stenosis unchanged. Postoperative CK levels were mildly decreased to 230-258 IU/L.

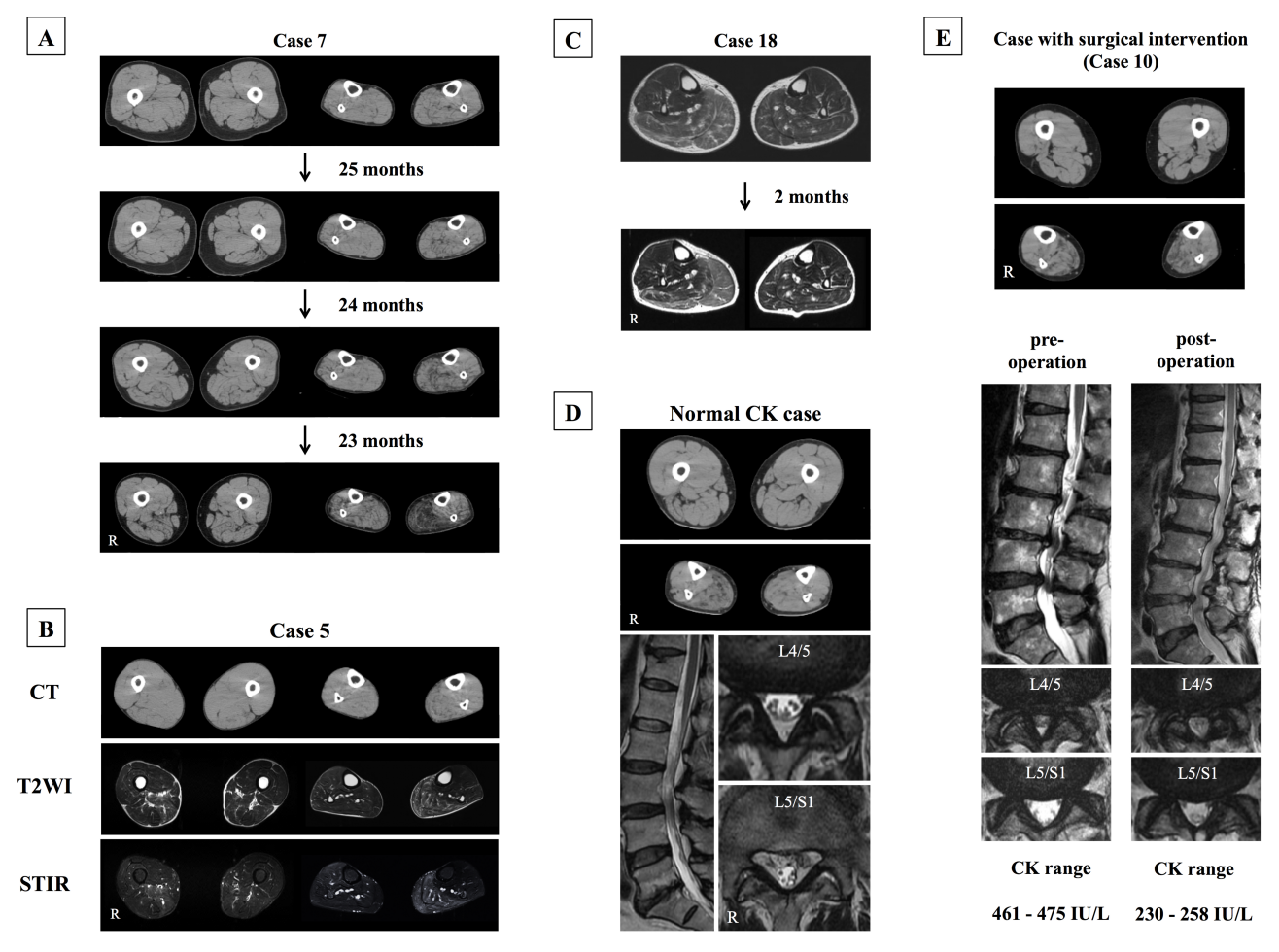
Figure 4.

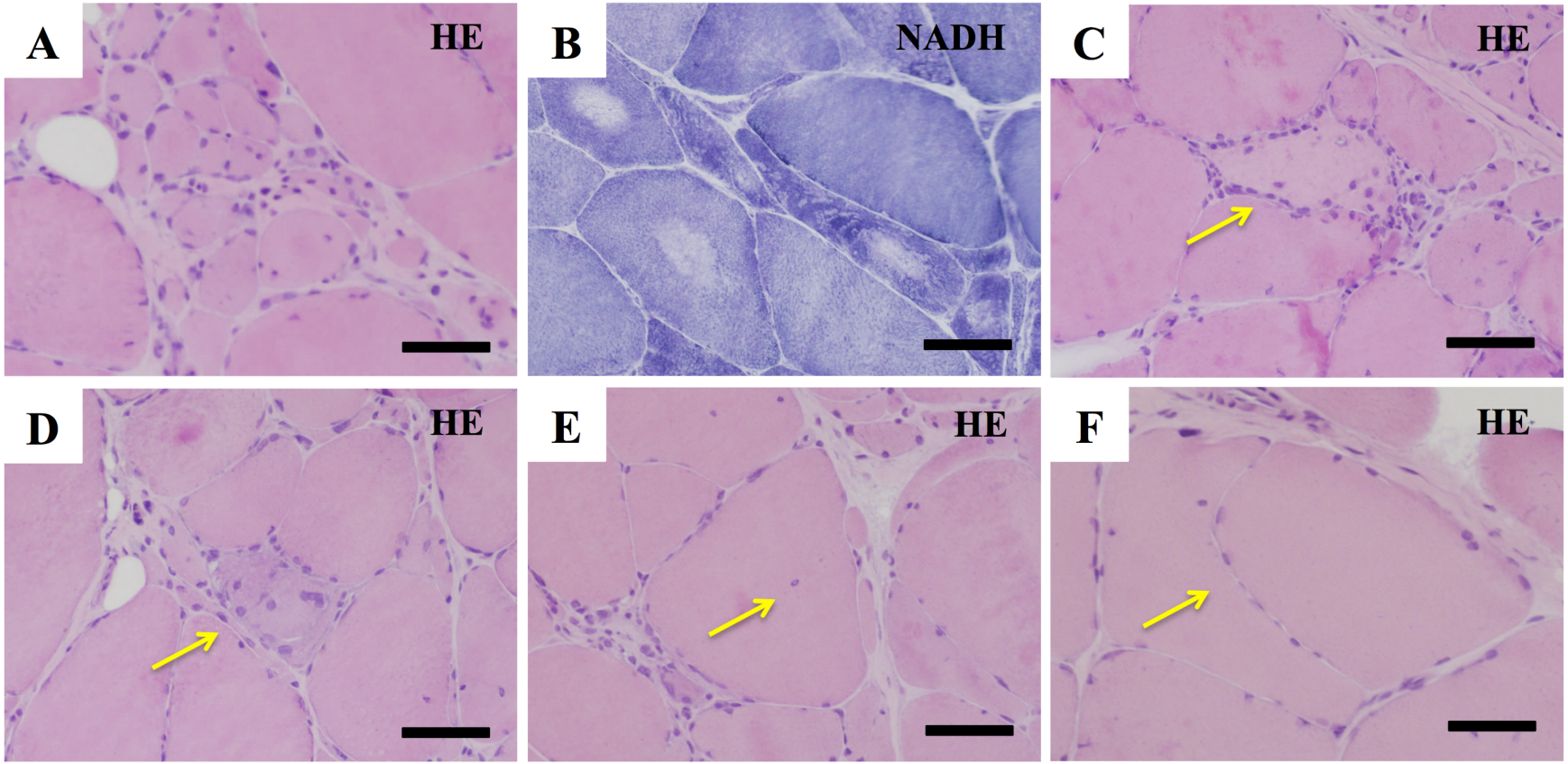
Representative histopathological findings of the NCACKEER case

Histopathological findings of muscle biopsy specimens with higher CK elevation (Case 7 in Table1, left and middle columns, right gastrocnemius muscle) are shown. The case had obvious neurogenic degenerative changes such as grouped atrophy of muscle fibers [A, hematoxylin and eosin (HE) staining] and target/targetoid fibers [B, beta-nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-TR) staining]. Case 7 also tended to have more necrotic fibers (C, arrow, HE staining), regenerating fibers (D, arrow, HE staining), central nuclei (E, arrow, HE staining), hypertrophic fibers, and fiber splitting (F, arrow, HE staining). Scale bar = 100 μm.


Case 3
Case 6
Case 7
R
L4/5
L5/S1
HE
Case 8
Case 15


Tibialis Anterior
Gastrocnemius medial head
MUP
2 mV
10 ms
Interference pattern
2 mV
0.1 s


A
Case 7
25 months
24 months
23 months
R
B
Case 5
CT
T2WI
STIR
R
C
Case 18
2 months
R
D
Normal CK case
R
L4/5
L5/S1
R
E
Case with surgical intervention
(Case 10)
R
pre-
operation
post-
operation
L4/5
L4/5
L5/S1
L5/S1
CK range
461 - 475 IU/L
CK range
230 - 258 IU/L


A
HE
B
NADH
C
HE
D
HE
E
HE
F
HE

Supplementary table 1

MRI analysis of parametric angles on spinal and sacral straightening in 18 NCACKEER cases

Characteristics	NCACKEER (n = 18)	control (n = 18)	*p*
Male, n (%)	13 (72)	13 (72)	1
Age, y, mean (SD)	65.6 (7.6)	62.1 (9.2)	0.24
Lumbar lordosis angle, mean (SD)	29.1 (9.8)	44.8 (9.1)	< 0.001
Sacral slope angle, mean (SD)	32.2 (7.2)	39.0 (7.8)	0.002

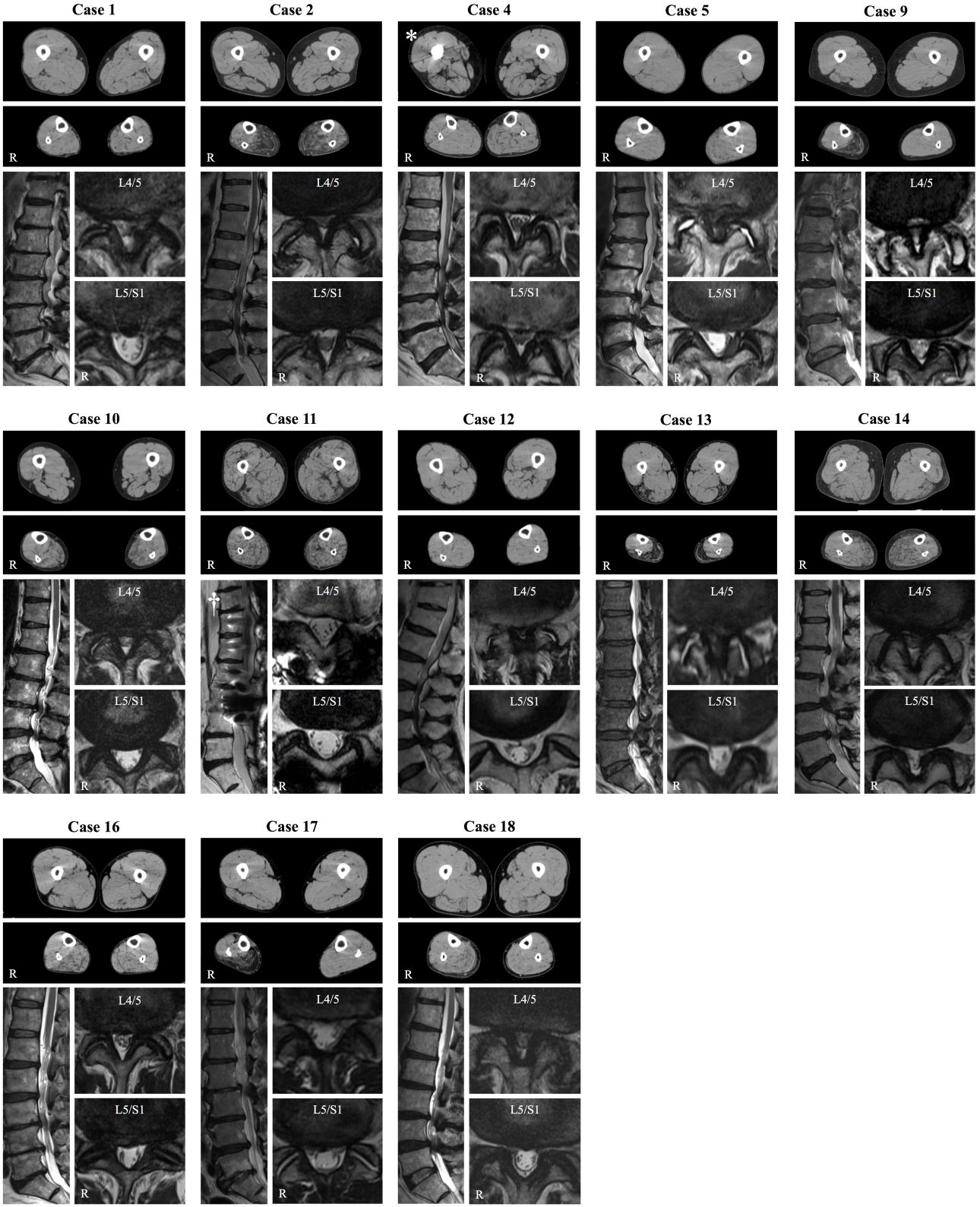
Abbreviations: **NCACKEER** = neurogenic calf amyotrophy with CK elevation by entrapment radiculopathy

Supplementary figure Legend

Supplementary figure 1.

Skeletal muscle CT and lumbar spinal MRI findings of 13 NCACKEER cases

Skeletal muscle CT images at the levels of middle thighs (upper row) and calves (middle row), lumbar spinal T2-weighted images at mid-sagittal (lower left column) and axial (lower right column) views at the levels of L4/5 and L5/S1 intervertebral foramina of 13 NCACKEER cases were shown with the same arrangement of items (Cases 1, 2, 4, 5, 9, 10, 11, 12, 13, 14, 16, 17, and 18 that shared the same case number in Table 1.). All cases exhibit calf amyotrophy on CT images. Axial MRI images showed L4/5 and/or L5/S1 intervertebral foraminal stenosis with or without various degrees of spinal canal stenosis in all cases. Sagittal MRI images showed spinal straightening in all cases to a certain degree. Case 4 had history of right artificial femoral head replacement (asterisk). Case 11 had history of posterior lumbar interbody fusion causing metal-artifacts on sagittal MRI (dagger).


Case 1
Case 2
Case 4
Case 5
Case 9
Case 10
Case 11
Case 12
Case 13
Case 14
Case 16
Case 17
Case 18
L4/5
L5/S1
R