Original Article

N-CAM Expression: The Study of Muscle Disease in a Tertiary Center of Thailand

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Background: Neural cell adhesion molecule (N-CAM), or CD56, is a cell-surface glycoprotein that plays a critical role in mediating intercellular adhesion in the central nervous system. It is also found to be expressed on embryonic muscle but disappears in healthy adult muscle. However, denervated or regenerating muscles can express N-CAM.

Objective: To evaluate the value of N-CAM expressions in diagnosing muscle diseases in the Thai population.

Materials and Methods: The present study used immunohistochemistry to interpret N-CAM expression in 75 muscle biopsy specimens diagnosed with myopathies and non-myopathies from a 3-year retrospective cohort.

Results: Using the chi-squared test, there was statistically significant associativity between N-CAM expression and the diagnosis of inflammatory myopathy, but not in muscular dystrophy, neurogenic change, or non-specific myopathy even though they also showed N-CAM expression. The inflammatory myopathy showed positive N-CAM in 15 out of 17 cases with statistical significance ($p<0.001$, OR 14.250, 95% CI 2.960 to 68.606). The authors did not find any N-CAM expression in the present study mitochondrial myopathy or non-myopathy cases, whose biopsies were defined as a control group due to lack of myopathic change and non-specific clinical symptoms.

Conclusion: The authors suggest the evaluation of N-CAM expression as a complementary tool in the diagnosis of muscle diseases that have denervated or regenerating muscle fibers, especially in inflammatory myopathy.

Keywords: Neural cell adhesion molecule; N-CAM; CD56; Muscle disease; Myopathy

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Muscle diseases or myopathies are neuromuscular disorders presented with symmetrical muscle weakness due to dysfunction of muscle fibers. Common muscle diseases include muscular dystrophy, congenital myopathy, mitochondrial myopathy, inflammatory myopathy, and neurogenic change[1]. Muscle biopsy is a useful tool for muscle disease diagnosis, but the pathological findings gained from the biopsies can vary from obvious to subtle myopathic changes that may be difficult to identify[2]. Immunohistochemistry (IHC) is an ancillary tool complementing the diagnosis of muscle diseases[3].

Neural cell adhesion molecule (N-CAM) is an integral membrane glycoprotein theorized to play distinct roles in myogenesis, synaptogenesis, and synaptic maintenance[4-7]. In embryonic muscle, N-CAM is transiently present on the surface of myotubes and myoblasts and intramuscular nerves. It is lost as the myotubes develop and the nerves become myelinated[8,9]. In normal adult muscle, N-CAM is not expressed on muscle fiber except in the portions that comprise the neuromuscular junction, where it is present on the surface of the muscle fiber and motor nerve and the portion perisynaptic Schwann cells capping nerve terminals[6]. Furthermore, there is evidence that N-CAM is expressed in satellite cells[10,11]. For abnormal muscle, it is demonstrated that N-CAM is expressed in regenerating and

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denervated muscle fibers, and research has been done to investigate its potential as a complementary tool in diagnosing muscle disease. Previous studies found that N-CAM is also presented in regenerating muscle fibers in myopathy[12] and showed an association between these muscle fibers in mitochondrial myopathies, inflammatory myopathies, and muscular dystrophies[12-14]. The presence of regenerating or denervated muscle fibers, combined with clinical information, can be used to diagnose muscle disease or myopathy[4,7,11,15,16].

The present study aimed to establish the N-CAM expression pattern and the association between N-CAM and regenerating fibers in common muscle diseases found in the Thai population, including muscular dystrophy, neurogenic change, inflammatory myopathy, mitochondrial myopathy, and non-specific myopathy. N-CAM is not included in the inflammatory IHC panel of the muscle biopsy. The authors hoped to investigate the potential of N-CAM expression in muscle diseases as a complementary tool for diagnostic evaluation because N-CAM expression is not yet routinely studied in Thailand.

Materials and Methods

Ethics approval and consent to participate

The protocol for the present study was approved by the Ethical Clearance Committee on Human Rights Related to Research Involving Human Subjects of the Faculty of Medicine Ramathibodi Hospital, Mahidol University (MURA) (COA no. 2019/721). All procedures performed in the present study that involved human participants were in accordance with the ethical standards of the Institutional or National Research Committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standard. Written informed consents were obtained from all participants in the present study.

Muscle specimens

A retrospective study was performed on all muscle biopsy specimens between 2017 and 2019 in Ramathibodi Hospital. Seventy-five clinical myopathy cases that had muscle biopsies were included in the present study. The diagnosis criteria were based on both clinical association and histologic findings. Clinical features and patient characteristics including age, gender, serum creatine phosphokinase level, and specimen site were obtained from the patients' medical records.

Histologic evaluation

Muscles from biceps brachii or quadriceps femoris in each case were collected as 2 cm-long specimens and divided into three parts. The first part was prepared fresh with the snap-frozen section technique. The second part was prepared in 10% neutral buffered formalin fixation. The third part was fixed in 3% glutaraldehyde for electron microscopic study. Only the first part, prepared with the snap-frozen section technique, was used in the present study.

The series of routine histochemical stains included hematoxylin and eosin (H&E), enzymatic histochemistry, and immunohistochemistry. The muscle biopsies were evaluated and correlated with clinical information to diagnosis.

In the present study, the authors used only biopsied muscle from snap frozen section to explore the N-CAM expression. The diagnoses of muscle diseases from clinical and histopathology findings were categorized as inflammatory myopathy, neurogenic change, muscular dystrophy, mitochondrial myopathy, non-specific myopathy, and non-myopathy. Inflammatory myopathy was diagnosed based on the clinical information and the biopsy findings of myopathic changes on H&E. This was a presence of variation in muscle fiber sizes, regenerating fibers, degenerated/pale necrotic fibers, increased in endomysial connective tissue, disturbed internal architectural fibers on NADH-TR stain, and the positivity in one or more of inflammatory panel IHC as MHC class I, MHC class II, MAC(C5b9), CDs (CD3, CD4, CD8, CD68, CD20, or CD138. Neurogenic change was diagnosed based on the clinical information and the biopsy findings of neurogenic changes on H&E, which was a presence of variation in muscle fiber sizes, regenerating fibers, degenerated/pale necrotic fibers, medium to large group atrophy or bimodal appearance, angulate muscle fibers with or without nuclear bags/clumps, target/targetoid fibers, increased in endomysial connective tissue, disturbed internal architectural fibers on NADH-TR stain, or fiber type grouping on ATPase. Muscular dystrophy was diagnosed based on the clinical information and the biopsy findings of dystrophic changes on H&E, which was a presence of variation in muscle fiber sizes, regenerating fibers, degenerated/pale necrotic fibers, abnormal fibers as split, whorled, lobulated, or ring fibers, increased in endomysial connective tissue or endomysial fibrosis with fat replacement, disturbed internal architectural fibers on NADH-TR stain, and the decreased or absent labelling in one or

more of muscular dystrophy panel IHC as dystrophin, dystrophin-glycoprotein complex, extracellular membrane proteins, and other membrane proteins. Mitochondrial myopathy was diagnosed based on the clinical information and the biopsy findings of myopathic changes on H&E, which was a presence of variation in muscle fiber sizes, regenerating fibers, degenerated/pale necrotic fibers, ragged red fibers on mGT, COX negative/deficient fibers on oxidative enzyme, and a presence of subsarcolemmal accumulation of abnormal mitochondrial of various shapes and sizes, with or without paracrystalline inclusion bodies on electron microscopy. Non-specific myopathy was diagnosed based on the clinical information of non-specific muscle disease and lack of myopathic change on muscle biopsy and normal appearance on histochemistry and IHC. Non-myopathy was diagnosed based on the clinical information of non-muscle disease and lack of myopathic change on muscle biopsy and normal appearance on histochemistry and IHC, which was the control group.

Immunohistochemical study

The muscle biopsy specimens were snap-frozen in isopentane, which the freezing point was at –150°C, and liquid nitrogen, which the boiling point was at –196°C, and were stored in a refrigerator at –80°C until use. Cryostat sections of 8-µm thick were cut and dried on glass slides at room temperature. The palatine tonsil tissue was used as a positive control on each slide. The staining was automatedly performed on Ventana BenchMark XT (Ventana Medical Systems Inc., Tucson, AZ, USA). Briefly, after blocking the endogenous peroxidase by the I-View Inhibitor (Ventana), samples were incubated at 36°C for one hour with anti-CD56 rabbit monoclonal primary antibody (clone MRQ-42, dilution 1:200, Cell Marque, MilliporeSigma, Rocklin, CA, USA). Antigen-antibody reactions were visualized using Ventana OptiView Amplification kit with OptiView HQ Linker for 12 minutes and OptiView HRP Multimer for 12 minutes. Counterstaining was obtained using Ventana Hematoxylin II for 16 minutes, followed by bluing reagent for four minutes. Finally, all slides were removed from the stainer, dehydrated, and coverslipped for microscopic examination under optical microscopy.

Interpretation

The N-CAM positivity was shown by the cytoplasmic staining in regenerating fibers. Generally regenerating fibers were easily identified by enlarged nuclei with a bluish stain sarcoplasm on H&E staining, as shown in Figure 1A. The bluish stain was due to the increased concentration of RNA within the cell[2]. Some regenerating fibers looked like normal fiber and were challenging to identify but showed positive N-CAM staining. For the present study, the N-CAM immunohistochemical results were divided into three groups, 1) when one or more muscle fibers were moderately to intensely cytoplasmic staining, the result was recorded as strongly positive stained, as shown in Figure 1B, 2) when one or more muscle fibers were faintly cytoplasmic staining, the result was recorded as weakly positive stained as shown in Figure 1D, and 3) when no fiber was stained, a negative result was recorded, as shown in Figure 1F. Since N-CAM was not expressed on normal adult muscle fiber, the authors used normal appearance muscle fiber or not injured, in the biopsy for the internal negative control[6,10] (Figure 1).

Statistical analysis

The relationship between N-CAM expression and common muscle diseases were evaluated using the chi-squared test. Odds ratios (ORs) were estimated in myopathies, which correlated with N-CAM expression.

The p-values less than 0.05 were considered statistically significant and ORs more than 1.0 indicated an increased risk among the compared muscle diseases, whereas ORs less than 1.0 indicated a decrease in risk in each muscle disease. All data were analyzed by using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristic

Of the 75 patients, 41 (54.66%) cases were females, and 34 (45.33%) cases were males. The mean age was 35 years, and the standard deviation was 25.54. The specimens were collected from quadriceps femoris in 59 (78.67%) cases and collected from biceps brachii in 16 (21.33%) cases.

Common muscle diseases

The most common diagnosis was non-specific myopathy with 35 (46.67%) cases, and the second most common diagnosis was inflammatory myopathy with 17 (22.67%) cases. There were nine (12.00%) neurogenic changed cases, seven (9.33%) muscular dystrophy cases, five (6.67%) non- myopathy cases, whose biopsies were defined as a control group

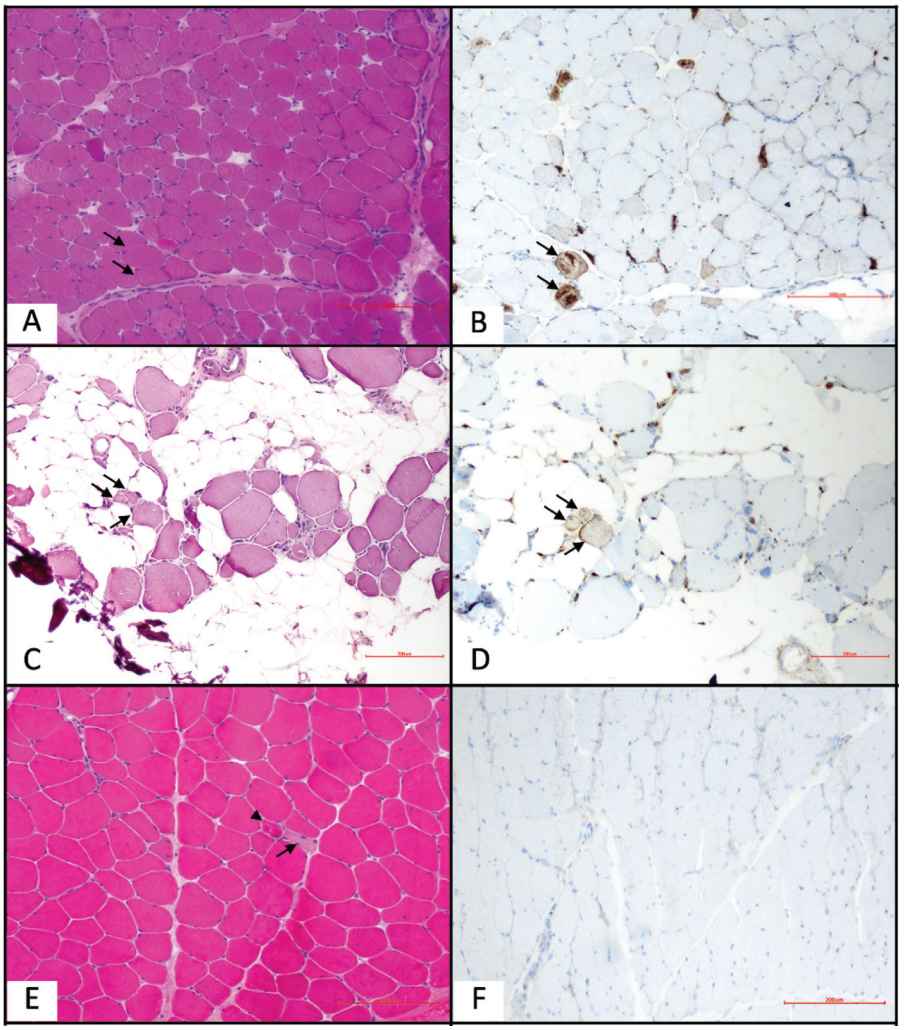

Figure 1. N-CAM interpretation.

Regenerating fibers, which sometimes were difficult to differentiate from normal muscle fibers on H&E, could be highlighted by immunohistochemistry against N-CAM. A. (H&E, 100X), H&E showed some bluish cytoplasmic fibers suggestive of regenerating fibers (black arrow). B. (N-CAM, 100X), N-CAM was strongly positive on the cytoplasm of all bluish regenerating fibers (black arrow) (A, B-same patient). Some additional regenerating fibers were mild to moderately highlighted by N-CAM, which initially were difficult to identify on H&E (in the center). Some scattered satellite cells were also highlighted by N-CAM, appearing as dense dot-like stained cells, close to the muscle fibers. C. (H&E, 100X), H&E showed fibers previously recorded as a few denervated/degenerated fibers without regenerating fibers (black arrow). D. (N-CAM, 100X), N-CAM was weakly positive on the cytoplasm of a few fibers thought to be denervated/degenerated fibers, which on review were regenerating fibers (black arrow). Some scattered satellite cells were also highlighted by N-CAM (C, D-same patient). E. (H&E, 100X), H&E showed a possibly regenerating fiber and one pale necrotic fiber near the center (black arrow). F. (N-CAM, 100X), N-CAM was absent on all fibers (N-CAM negative). The pale necrotic and possibly regenerating fibers were not expressed N-CAM, and the possibly regenerating fiber was interpreted on review as a degenerated fiber. This representative specimen was from the non-myopathy patient (E, F-same patient).

due to lack of myopathic change and non-muscle disease clinical symptoms, and two (2.67%) cases of mitochondrial myopathy as shown on Table 1.

Association between muscle diseases and N-CAM expression

The result of N-CAM expression showed positive staining in 35 cases and negative staining in 40 cases.

The inflammatory myopathy showed positive N-CAM in 15 out of 17 cases with statistical significance ($p<0.001$, OR 14.250, 95% CI 2.960 to 68.606). N-CAM was also positive in muscular dystrophy, neurogenic change, and non-specific myopathy, but was not statistically significant in p-value. No positive N-CAM was found in mitochondrial myopathy and non-diagnostic myopathy or the control group, as shown in Table 2 and 3.

The authors also correlated the positive group with the presence of regenerating fibers in

Table 1. Summary of patient characteristics

	Total (n=75); n (%)	Male [34 (45.33)]; n (%)	Female [41 (54.67)]; n (%)
Age group			
≤20	29 (38.67)	14 (41.18)	15 (36.59)
21 to 30	6 (8.00)	6 (17.65)	0 (0.00)
31 to 40	6 (8.00)	1 (2.94)	5 (12.20)
41 to 50	9 (12.00)	1 (2.94)	8 (19.51)
51 to 60	9 (12.00)	2 (5.88)	7 (17.07)
>60	16 (21.33)	10 (29.41)	6 (14.63)
Diagnosis			
Non-specific myopathy	35 (46.67)	16 (47.06)	19 (46.34)
Inflammatory myopathy	17 (22.67)	5 (14.71)	12 (29.27)
Neurogenic change	9 (12.00)	3 (8.82)	6 (14.63)
Muscular dystrophy	7 (9.33)	6 (17.65)	1 (2.44)
Mitochondrial myopathy	2 (2.67)	1 (2.94)	1 (2.44)
Non-myopathy	5 (6.67)	3 (8.82)	2 (4.88)

Table 2. Categorization of muscle disease and its correlation with N-CAM expression

N-CAM expression	Categorization of muscle diseases (n=75); n (%)					
	Muscular dystrophy	Neurogenic change	Inflammatory myopathy	Mitochondrial myopathy	Non-specific myopathy	Non-myopathy
Positive	6 (85.71)	4 (44.44)	15 (88.24)	0 (0.00)	10 (28.57)	0 (0.00)
p-value	0.050	0.887	<0.001	-	0.003	-
ORs	8.069	0.903	14.250	-	0.240	-
95% CI	0.920 to 70.734	0.223 to 3.666	2.960 to 68.606	-	0.091 to 0.635	-
Negative	1 (14.29)	5 (55.56)	2 (11.76)	2 (100)	25 (71.43)	5 (100)

N-CAM=neural cell adhesion molecule; ORs=odds ratios; CI=confidence interval

Table 3. Categorization of muscle disease and characteristics of N-CAM expression

Characteristics of N-CAM expression	Categorization of muscle disease (n=35); n (%)					
	Muscular dystrophy	Neurogenic change	Inflammatory myopathy	Mitochondrial myopathy	Non-specific myopathy	Non-myopathy
Staining grade						
Weak	1 (16.67)	4 (100)	4 (26.67)	-	8 (80.00)	-
Strong	5 (83.33)	0 (0.00)	11 (73.33)	-	2 (20.00)	-
Regenerating fibers						
Absent	0 (0.00)	0 (0.00)	0 (0.00)	-	0 (0.00)	-
Present	6 (100)	4 (100)	15 (100)	-	10 (100)	-

N-CAM=neural cell adhesion molecule

histology. All positive cases showed regenerating fibers in the muscle biopsies. The strongly positive N-CAM mostly appeared in inflammatory myopathy and muscular dystrophy. The weakly positive N-CAM appeared in neurogenic change and non-specific myopathy.

Discussion

N-CAM accumulates in regenerating and denervated fibers but is not necessarily expressed in muscle diseases[8]. In a study on the expression of N-CAM in mitochondrial myopathy by Heuss et al in 1995, it was discovered that muscle fibers are N-CAM-positive but do not appear as ragged red fibers or as cytochrome C oxidase deficient, while all the ragged red fibers or cytochrome C oxidase deficient fibers were N-CAM-positive. This may suggest that the expression of N-CAM precede the

manifestation of morphological or enzyme defects, or the technique used to identify N-CAM expression is more sensitive than those used to identify ragged red fibers and cytochrome C oxidase deficient fibers[12].

Double-staining with anti-vimentin and anti-N-CAM can be used to identify denervated muscle fibers, which show as vimentin-negative and N-CAM-positive, from regenerating muscle fibers, which show as vimentin-positive and N-CAM-positive[13].

There are isoforms of N-CAM, and the isoform expressed can be used to identify the type of fiber by the usage of polysialylation-specific antibodies. Non-activated cells like satellite cells and denervated fibers express only non-sialylated isoforms of N-CAM while regenerating fibers express N-CAM and their sialylated isoforms on the cell membrane and cytoplasm[10].

N-CAM-positive muscle fiber has been included as one of the suggestive muscle biopsy findings for dermatomyositis according to the 239th European Neuromuscular Centre (ENMC) international workshop classification in 2018[17].

All positive N-CAM cases had regenerating muscle fibers on hematoxylin and eosin slides. There were two cases of discordance. One case had been recorded as denervated/degenerated fibers without regenerating fibers but were weakly positive N-CAM, which is the the case in Figure 1C and D. The other case had been recorded as one possibly regenerating fiber and one pale necrotic fiber, which were negative N-CAM, which is the case in Figure1E and F. On the slide review, the authors had a consensus that the former case had regenerating fibers, and the latter case had no regenerating fibers. The present study did not have any case where regenerating fibers were shown in histology but not detected in N-CAM positivity.

In the present study, inflammatory myopathy had statistically significant associations with N-CAM expression in muscle fibers. Inflammatory myopathy showed N-CAM-positivity in 15 out of 17 cases ($p<0.01$) with an odds ratio of 14.250 (95% CI 2.960 to 68.606). Muscular dystrophy showed N-CAM-positivity in six out of seven cases ($p=0.050$), however, an odds ratio of 8.069 (95% CI 0.920 to 70.734). Regenerating fiber, which appears as a morphologically normal fiber on hematoxylin and eosin stain and other histochemistry, can be highlighted by immunohistochemistry against N-CAM.

The authors also found inflammatory myopathy and muscular dystrophy groups had strong-intensity immunohistochemistry against N-CAM at 73% and 83%, respectively.

The present study only had two mitochondrial myopathy cases. All the cases showed negative immunohistochemistry for N-CAM. Their hematoxylin and eosin sections were also absent for regenerating fibers. These results are limited for evaluation due to the small sample size of the specimen. The small sample may be the reason for the discrepancy between the present study and a previous study by Heuss et al in 1995[12].

Conclusion

Within the present study, inflammatory myopathy showed a statistically significant association with positive N-CAM expression, and alongside muscular dystrophy, are the groups that showed strongly positive N-CAM. Weakly positive N-CAM expression was found in neurogenic change and non-specific myopathy. Negative N-CAM expression was found in mitochondrial myopathy and non-myopathy.

N-CAM helped to detect regenerating muscle fibers in the present study and may help to distinguish regenerating fibers from denervated/degenerated muscle fibers, as shown in Figure 1C to F. However, the present study had a limitation for interpretation because it is not using double staining with anti-vimentin and anti-N-CAM[13].

The authors concluded that N-CAM expression can be a useful complementary tool in diagnosing muscle diseases with regeneration or denervation of muscle fibers. The authors recommend further study in a larger group.

What is already known on this topic?

N-CAM expression in re-innervated muscle fibers of neurogenic change has been proposed.

What this study adds?

N-CAM expression can be a useful complementary tool in diagnosing muscle diseases with regeneration or denervation of muscle fibers.

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Availability of data and materials

All data were presented in this paper and there are no additional supporting files. The hematoxylin and eosin-stained and immunohistochemical slides were stored at the Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Mahidol University.

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Conflicts of interest

The authors declare no conflict of interest.

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