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*Original Article*

# Pathological findings in sporadic inclusion body myositis and GNE myopathy

Yutong Zhang[1], Chuanqiang Pu[1], Xianghui Lu[1], Qiang Shi[1], Huifang Wang[1], Rui Ban[1,2], Huaxu Liu[1], Miaomiao Wei[1,2], Haiwen Song[1,2]

[1]*Department of Neurology, PLA General Hospital, Beijing, China;* [2]*School of Medicine, Nankai University, Tianjin, China*

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**Abstract:** Objective: The following study compared the pathological findings between sporadic inclusion body myositis (sIBM) and Glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase myopathy (GNEM) patients. Methods: An enzyme histochemistry was used to compare the pathological characteristics between 11 patients with sIBM and 16 patients with GNEM. Results: There were four pathological differences observed: (1) A majority of the rimmed vacuoles found in the sIBM patients resembled cracks, whereas the GNEM patients ($P$=0.004) had round or oval vacuoles. (2) A majority of the rimmed vacuoles that were located in the periphery of the atrophic muscle fibers of the sIBM patients. The patients with GNEM had a majority of the rimmed vacuoles in the center of the atrophic muscle fibers ($P$=0.001). (3) The patients with sIBM had basophilic granules in the rimmed vacuoles, which appeared to be fine granules that were sand-like particles. The GNEM patients had coarse granules ($P$=0.018). (4) The proportion of mononuclear cells invasion of muscle fibers was larger in the sIBM patients than the GNEM patients ($P$=0.047). The GNEM patients were younger on average than the sIBM patients at the onset of symptoms ($P$<0.001) and at the diagnosis age ($P$<0.001). The electromyography (EMG) showed the presence of myogenic lesions in 10 patients with sIBM, both myogenic and neurogenic lesions in one patients with sIBM and myogenic lesions in 16 patients with GNEM. Conclusion: There were significant differences in the morphologies of the rimmed vacuoles between sIBM patients and GNEM patients.

**Keywords:** sIBM, GNEM, muscular pathology

## Introduction

Sporadic inclusion body myositis (sIBM) is the most common acquired myopathy for patients over age 50 [1]. sIBM is a chronic progressive inflammatory disorder in that effects skeletal muscle. It is clinically characterized by early and often asymmetric muscular weakness and atrophy [2]. The major pathological features of sIBM are inflammation and rimmed vacuoles found in muscle biopsies and inclusion bodies found in ultrastructural studies. UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase gene (GNE) myopathy is an autosomal recessive hereditary inclusion body myopathy (hIBM) [3]. GNE-hIBM is an early adult-onset myopathy, which primarily results in distal lower limb weakness and atrophy, however the quadriceps remain relatively unaffected [4]. The muscle pathology of GNE myopathy is similar to sIBM, except for focal inflammation in sIBM patients [5].

There are not many differences found in the clinical and pathological manifestations of sIBM and GNE myopathy. This remains consistent under electromyograph (EMG), where they exhibit similar changes [6]. The inflammatory changes in pathology can be patchy in the muscle biopsy of sIBM, which is also found in GNE myopathy biopsies [7-9]. This makes the diagnostic process difficult. There is no known published research that addresses the distinctions of pathomorphism between the two myopathies. In the following study, the pathological features of sIBM are compared to the features found in GNE myopathy in order to identify the differences that could be helpful in determining the clinical differential diagnosis.

## Materials and methods

### *Subjects*

Eleven patients were diagnosed with sIBM and 16 patients with GNE myopathy in the neuropa-

**Table 1.** Comparison of serum kinase data between sIBM and GNE myopathy patients

| | CK | | | | LDH | | | |
|---|---|---|---|---|---|---|---|---|
| | n | | Values (U/L) | P | n | | Values (U/L) | P |
| | Normal | Elevatory | | | Normal | Elevatory | | |
| sIBM | 4 (36%) | 7 (64%) | 427.05±395.28 | 0.057 | 8 (72.7%) | 3 (27.3%) | 199.13±50.13 | 0.077 |
| GNE | 2 (12.5%) | 14 (87.5%) | 900.66±814.24 | | 9 (56.3%) | 7 (43.7%) | 250.68±82.60 | |

CK, serum creatine kinase; LDH, lactate dehydrogenase; n, number of subjects.

thology laboratory of the Chinese People's Liberation Army General Hospital from October 2003 to October 2016, in accordance to the Grigg's canonical pathologic criteria for sIBM [10] and Gene screening.

*Clinical data collection*

The study protocol data collected from all patients included: (1) Detailed general history: gender, age at onset, age at diagnosis, initial symptoms or signs, clinical course, and family history. (2) Laboratory data: serum creatine kinase (CK), lactate dehydrogenase (LDH), electromyography (EMG), and muscle biopsy.

*Enzyme histochemical studies*

Muscle samples were frozen in liquid nitrogen immediately after removal and stored at -80°C. Transverse serial frozen muscle sections were stained with hematoxylin and eosin (H&E), Gomori trichrome stain (MGT), oil red O (ORO), periodic acid-Schiff (PAS), nicotinamide adenine dinucleotide dehydrogenase (NADH), nonspecific esterase (NSE), and adenosine triphosphatase (ATPase). The morphometric evaluation of muscle specimens was performed under a light microscope.

*Statistical analysis*

The Continuous variables were presented as mean ± SD and analyzed using an independent t test and a 1-way analysis of variance. Dichotomous variables were evaluated using the Fisher's exact test. All statistical tests were two-tailed. P<0.05 was considered as statistically significant. All statistical analyses were performed with SPSS18.0 statistical software.

## Results

*Onset age*

Among the 11 patients with sIBM, 8 were male (72.73%) and 3 were female (27.27%). The onset age ranged from 38 years to 71 years (51.09±9.56 years). The diagnosis age ranged from 41 years to 76 years (56.09±11.12 years). The time between onset to diagnosis ranged from 1 year to 14 years (5.00±3.77 years). Among the 16 patients with GNE myopathy, 13 were male (81.25%) and 3 were female (18.75%). The onset age ranged from 2 years to 43 years (25.88±11.30 years). The diagnosis age ranged from 20 years to 53 years (32.00±9.60 years). The time between onset to diagnosis ranged from 0.5 years to 20 years (6.06±5.9 years). As expected, the GNE myopathy patients were significantly younger than sIBM patients at the onset of the symptoms ($P$=0.000003) and at the diagnosis age ($P$=0.000003). However, the time between onset and diagnosis were similar ($P$=0.608).

*Laboratory examinations*

The EMG reports showed that there were 10 sIBM cases (90.9%) with myogenic lesions, one sIBM case (9.1%) with both myogenic lesions and neurogenic lesions, and 16 GNE cases (100%) with myogenic lesions.

The analysis of the serum kinase data (**Table 1**) showed that there were no statistical differences between the two groups for the CK level ($P$=0.057) and the LDH level ($P$=0.077).

*Myopathological features*

The comparison of pathological features between sIBM patients and GNE myopathy patients are summarized in **Table 2**. The enzyme histochemical studies showed many similarities between the two. There were atrophic fibers that were a small round shape, with angularity or irregularity, some internal nuclei within the fibers, with disintegration, as well as hypertrophy of the fibers. There were red staining granules found in all samples that were stained via Gomori trichrome. Additionally, the three sIBM (27.3%) samples and the one GNE sample (6.25%) showed inflammatory cell infiltration, with no statistical difference between them.

**Table 2.** Comparison of the pathological findings between sIBM and GNE myopathy patients

| Pathological | Finding | sIBM, n (Percentage) | GNE, n (Percentage) | P |
|---|---|---|---|---|
| Morphous of atrophic muscle fiber | Small round | 1 (9.1%) | 1 (6.25%) | |
| | Small angular | 6 (54.5%) | 8 (50%) | 1.000 |
| | Irregular | 4 (36.4%) | 7 (43.75%) | |
| Morphous of rimmed vacuoles | Crack | 5 (45.4%) | 0 (0%) | |
| | Round or oval | 2 (18.2%) | 11 (68.75%) | 0.004 |
| | Crack, round and oval | 4 (36.4%) | 5 (31.25%) | |
| Location of rimmed vacuoles in atrophic muscle fiber | Mainly in center | 1 (9.1%) | 12 (75%) | 0.001 |
| | Mainly in periphery | 10 (90.9%) | 4 (25%) | |
| The largest number of rimmed vacuoles in one cell | 1-2 | 9 (81.8%) | 8 (50%) | 0.124 |
| | ≥3 | 2 (18.2%) | 8 (50%) | |
| Basophilic granules in rimmed vacuoles | Fine granules mainly | 9 (81.8%) | 5 (31.25%) | 0.018 |
| | Coarse granules mainly | 2 (18.2%) | 11 (68.75%) | |
| Muscle fiber type | Equal distribution of muscle fiber type | 8 (72.7%) | 8 (50%) | |
| | Type I fiber dominantly | 1 (9.1%) | 4 (25%) | 0.566 |
| | Type II fiber dominantly | 2 (18.2%) | 4 (25%) | |
| Mononuclear cell invasion of muscle fiber | | 9 (81.8%) | 6 (37.5%) | 0.047 |
| Inflammatory cell infiltration | | 3 (27.3%) | 1 (6.25%) | 0.273 |
| RRF | | 3 (27.3%) | 0 (0%) | 0.056 |
| Internal nuclei within fiber | | 9 (81.8%) | 14 (87.5%) | 1.000 |
| Muscle fiber hypertrophy and split | | 10 (90.9%) | 14 (87.5%) | 1.000 |

n, number of subjects; RRF, ragged-red fibers.

There were four main differences found between the sIMB and GNE patients. Most of rimmed vacuoles resembled cracks (**Figure 1A-C**) in sIBM patients, whereas round or oval vacuoles were found (**Figure 1F-L**) in the GNE myopathy patients ($P$=0.004). The majority of rimmed vacuoles were located in the periphery of the atrophic muscle fibers (**Figure 1A-E**) in the sIBM patients, but were in center of the atrophic muscle fibers (**Figure 1G-L**) in the patients with GNE myopathy ($P$=0.001). The basophilic granules in the rimmed vacuoles were fine granules (**Figure 1A-E**) that were sand-like particles in the patients with sIBM, but they appeared to be coarse granules (**Figure 1F**, **1G**, **1I**, **1J**) in the GNE myopathy patients ($P$=0.018). The proportion of mononuclear cell invasions observed in the muscle fibers were larger in the sIBM patients than the GNE myopathy patients ($P$=0.047). There were no statistical differences between the two groups among the other aspects of pathologic findings ($P$>0.05).

## Discussion

GNE myopathy is both clinically and genetically heterogeneous, which includes vacuolar myopathy sparing quadriceps (VMSQ) in Iranian Jews [4] and distal myopathy with rimmed vacuoles (DMRV) in Japanese individuals [11]. hIBM solely refers to GNE myopathy in some literature [12] that shares clinical and histopathological features with sIBM, a commonly acquired muscle disease. For the purpose of differential diagnosis, GNE myopathy was taken as a representative of hIBM, and was compared with sIBM in order to study the muscular pathology.

The results of this study showed that males had a higher prevalence than females for both sIBM and GNE myopathy. The GNE myopathy patients were much younger than the sIBM patients at the onset of the disease, which was consistent with previously reported research [10, 13]. Both the sIBM and the GNE myopathy patients had myopathic EMG changes. Only one sIBM patient had mixed myopathic and neurogenic changes, which could be due to many factors [14, 15]. Moreover, the mean CK and LDH values were not statistically different between the two groups. This was different from the results of Mohamed Kazamel's study [6], which suggested that the laboratory data could be different between Asian patients and European patients, or that the results were limited by the number of patients within the current study. Overall, the validity of the CK and the LDH values for differential diagnostic process requires further research.

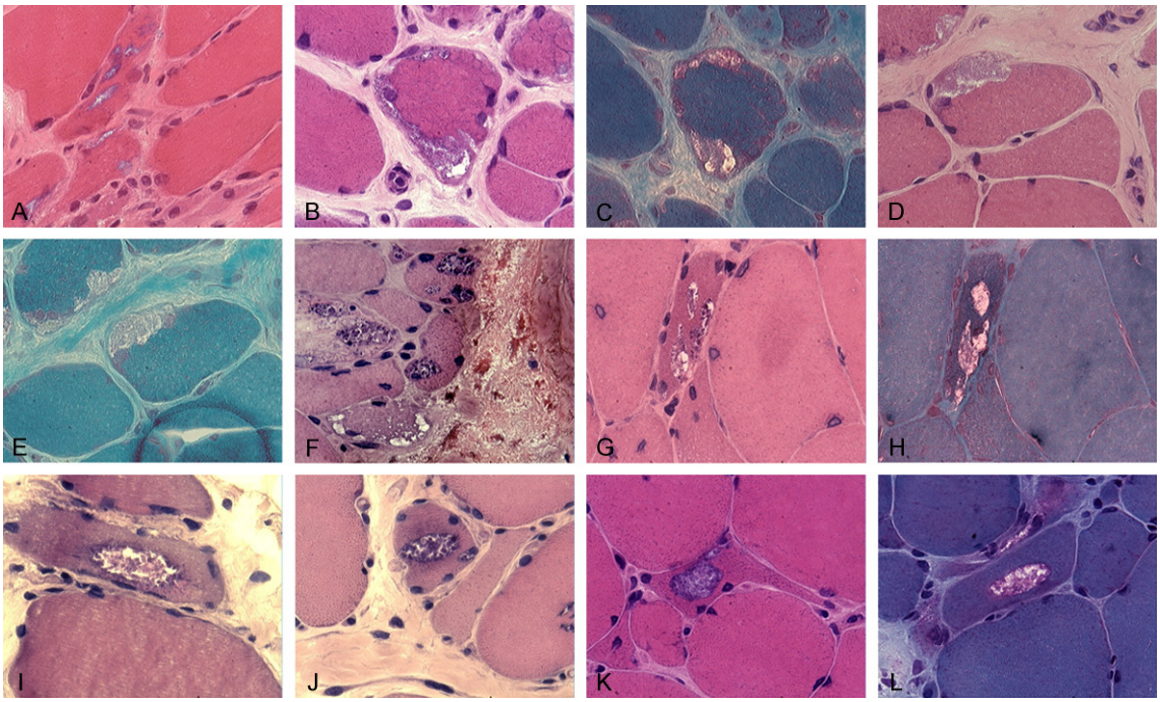


**Figure 1.** The rimmed vacuoles resembled cracks and the basophilic granules appeared to be fine granules in a sIBM patient (A: HE, ×400). The fiber was surrounded by rimmed vacuoles in a sIBM patient (B: HE, ×400; C: MGT, ×400). The rimmed vacuoles were located in the periphery of the fibers in a sIBM patient (D: HE, ×400; E: MGT, ×400). Rimmed vacuoles that were round and the granules appeared to be coarse granules in GNE myopathy patients (F: HE, ×400; G: HE, ×400; I: HE, ×400; J: HE, ×400). Some oval rimmed vacuoles that were located in center of the atrophic muscle fibers were observed in patients with GNE myopathy (G: HE, ×400; H: MGT, ×400; I: HE, ×400; J: HE, ×400; K: HE, ×400; L: MGT, ×400).

The pathologic findings had similarities between the two groups, which included vacuolated muscle fibers, basophilic inclusions in the rimmed vacuoles, equal distribution of the muscle fiber types in most cases, internal nuclei within the fibers, muscle fiber hypertrophy and splitting, and changes in the atrophic muscle fibers that were typically small, angular, and irregular. In addition, the inflammatory cell infiltration was detected in one GNE myopathy patient and 3 sIBM patients. The proportion of sIBM patients with inflammatory cells was not large within the Chinese patient population. The GNE myopathy patients could show inflammatory cell infiltration, which meant that the inflammatory changes were not useful in differential diagnosis [7-9]. The primary dissimilarity between the two groups was the morphological features of the rimmed vacuoles. In sIBM patients, the majority of the rimmed vacuoles were located in periphery of the atrophic muscle fibers. They resembled cracks and the basophilic granules in the rimmed vacuoles were fine granules. However, in patients with GNE myopathy, the majority of the rimmed vacuoles were located in center of the atrophic muscle fibers, and were round or oval with the basophilic granules in the rimmed vacuoles being coarse granules. The proportion of mononuclear cell invasions in the muscle fibers was larger in sIBM patients than the GNE myopathy patients. These pathological differences could contribute to the diagnosis.

In conclusion, there was a significant difference between the sIBM patients and the GNE myopathy patients found in the morphologies of the rimmed vacuoles. There were a small number of patients in this study and further pathologic analysis is needed. An efficient combination of clinical manifestation, laboratory examination results, and histopathological findings are necessary for a final diagnosis.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Chuanqiang Pu, Department of Neurology, The Chinese People's Liberation Army General Hospital, 28 Fuxing Road, Beijing 100853, China. Tel: +86 13910269169; Fax: +86 1066939251; E-mail: pucq30128@sina.cn

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