대한병리학회지 : 제20권 제 3 호
K. J. Path., 20(3) : 328, 1986

☐ **Brief communication** ☐

Myotubular myopathy

—A case report—

Je G. Chi, M.D.

Department of Pathology, Seoul National University Children's Hospital and College of Medicine, Seoul National University

A case of a myotubular myopathy in a 5 year old boy is described. This was the first and the only boy to a 30 year old mother who had no prenatal or perinatal problems. No family history of muscle disease was present. His muscle weakness started from neonatal period but was very slowly progressive. The developmental milestones were generally delayed. He had repeated episodes of pneumonia.

Muscle biopsy revealed characteristic central nuclei in 68% of myofibers, and this finding was associated with generally small and round fibers and minimal interstitial change. No inflammatory reaction was present.

Key Words: Myotubular myopathy, congenital myopathy, centronuclear myopathy.

Myotubular myopathy, also called centronuclear myopathy is a very rare congenital myopathy characterized by progressive generalized muscle weakness often including ptosis and weakness of the extraocular muscles. By 1985, more than 60 cases of myotubular myopathy or centronuclear myopathy have been recorded in the literature (Kakulas and Adams, 1985)[1]. However, no such case can be searched in Korean literature. This disease is microscopically characterized by centrally displaced nuclei in 45 to 50% of otherwise normal myofibers. This central displacement is reminiscent of fetal muscle in myotubular phase, thus the term myotubular myopathy was named.

This case report deals with a 5 year old boy who had recurrent pneumonias and generalized muscle weakness since birth and was found to have myotubular myopathy by muscle biopsy. The patient was the product of full term vacuum extracted delivery to a 30 year old mother who had no specific problems during the pregnancy. There was no family history of muscle disease. And this was the only child. Immediately after birth initial crying was good. At 3 months of age the mother noted poor weight gain. The developmental milestones including head control, crying and standing were delayed considerably. He could barely roll over at 4 months of age. On August 1981, at his age of $1^1/_2$ year he was admitted to Pusan University Hospital for motor retardation, where he was placed on synthyroid under the diagnosis of congenital hypothyroidism. Brain CT done at that time was normal. After taking synthyroid for 6 months there was no improvement of muscle power. For 3 years after birth he had had pneumonia more than 10 times, for which he was hospitalized for 3 times.

On February 24, 1984, he first came to Seoul National University Hospital and was followed ever since. It was first noted that he had suffered from chronic malnutrition, and was placed on Linavar (Oxandrolene). However, over the ensuing 9 months, despite weight gain and improved appetite, muscle atrophy was progressive. Pectoralis muscle was particularly wasted, and elbow joint hyperextension

was also noted. Chest and skull roentgenograms were normal. Physical examination at admission on August 6, 1985 showed a pale lean boy with body weight of 14.5 kg (3-10 p), height 110 cm (50-75 p), head circumference 50.5 cm (50-70 p), and abdominal circumference 49 cm. Blood pressure was 110/70 mmHg, body temperature 36.0℃ and pulse rate 100/min. The head was normocephalic. The pupils were equal in size and light reflex was prompt. The neck was supple. The chest was symmetrical, and there were clear breathing sound and regular heart beats. The abdomen was soft and flat. The liver was 1 fingerbreadth palpable and the spleen was impalpable. Genitalia showed relatively large phallus. Both testes were normal in size. There was no pitting or clubbing fingers. Both thumbs and little fingers were relatively longer. The muscle atrophy was marked at shoulder, arm and forearm. There was hypertrichosis of the back skin. Neurological examination showed cranial nerves all intact. Muscle power was decreased considerably in neck (flexion) and shoulder (elevation, flexion and external rotation). It was weak in hip (flexion and external rotation). Sensory modalities were all within normal limits. Deep tenden reflexes were generally decreased. No pathological reflexes were elicited. No fasciculation noted.

Laboratory findings were as follows; Hemoglobin 14.0 gm/dl, hematocrit 40.9%, WBC 7800/mm³ with 36% segmented, 47% lymphocytes, 11% monocytes, 6% eosinophils. Platelet was 326000/mm³. Blood chemistry showed Ca 9.8 mg%, P 5.6 mg%, CPK 141 IU/L; LDH 348 IU/L. X-ray films showed cervicolumbar scoliosis and osteoporosis of feet. Electromyography showed normal motor unit potential and many polyphasic potentials with small amplitude and short duration. Thyroid function tests and serum immunoglobulins were all reported normal. Muscle biopsy was done at rectus femoris on August 8, 1985.

Microscopically the myofibers were generally

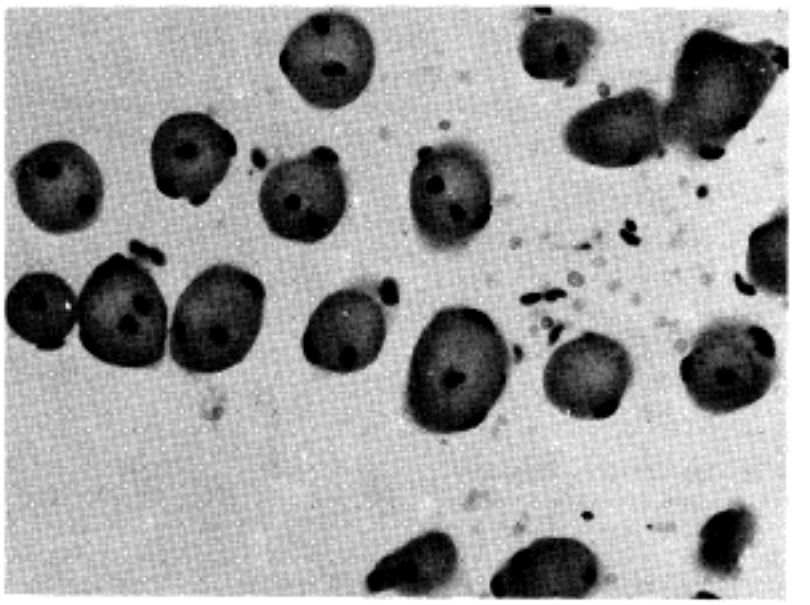

Plate. 1. Myotubular myopathy, revealing a characteristic feature of central nuclei in most myofibers. H&E ×200

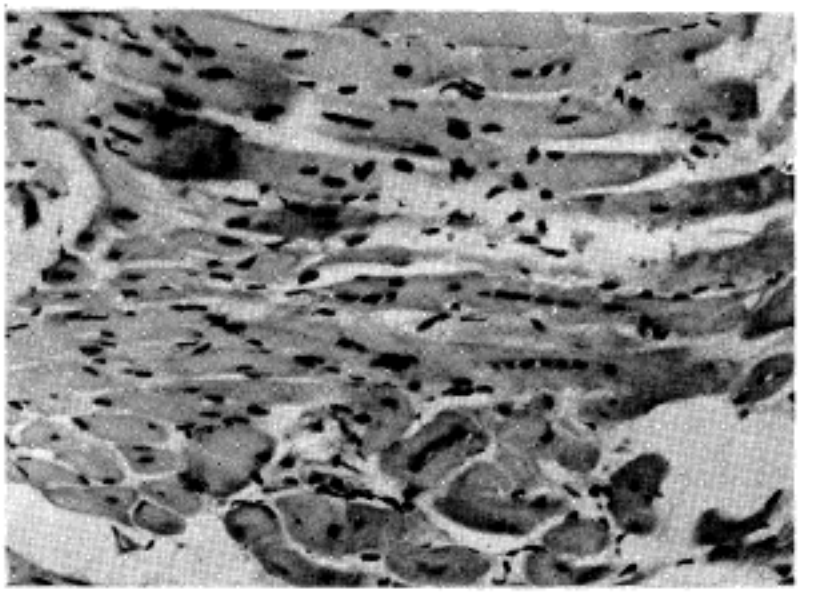

Plate. 2. Longitudinal section of muscle biopsy, showing centrally displaced sarcolemmal nuclei often forming chain nuclei. H&E ×100

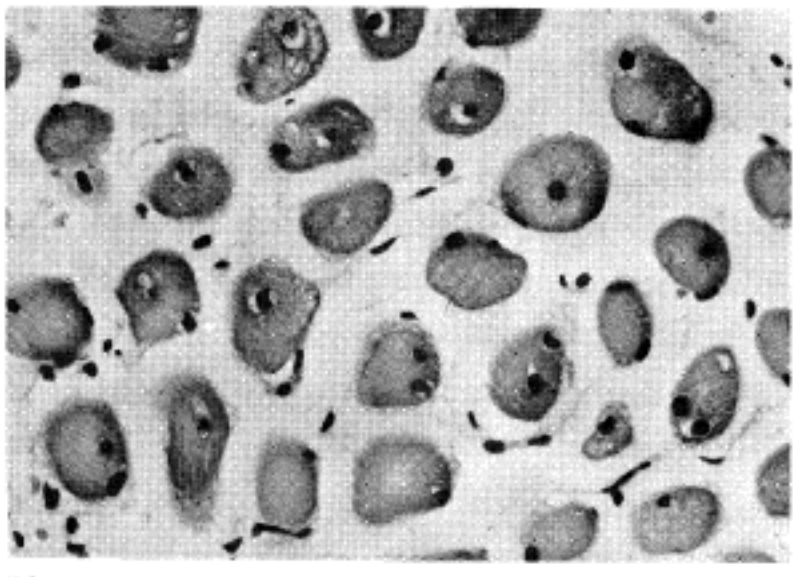

Plate. 3. Photomicrograph of muscle biopsy. One or two nuclei are seen in cross-sectioned round fibers. Interstitial widening is partly artefactual. H&E ×200

Table 1. Proportion of central nuclei in the muscle specimen in this case

Central nuclei	Number (%)
Myofibers	100
with central nuclei	68
a) 1 nucleus	41
b) 2 nuclei	21
c) 3 nuclei	5
d) 4 nuclei	1
with no central nucleus	32

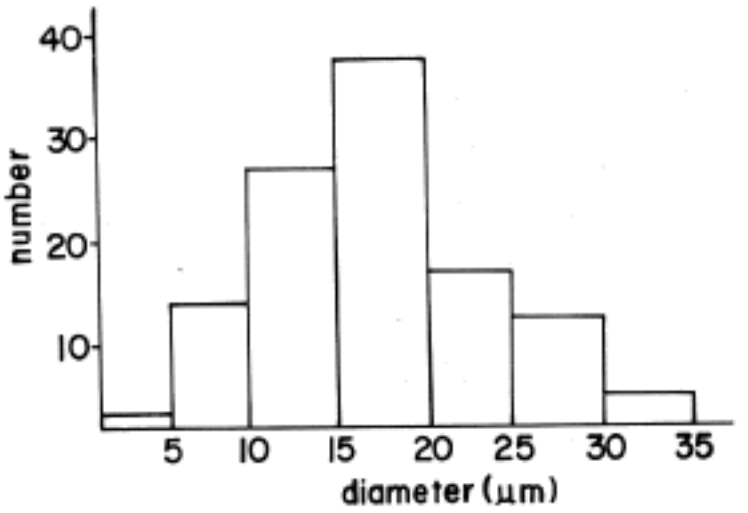

Fig. 1. Histogram of fiber size shows mostly smaller fibers with occasional very small or relatively normal ones.

smaller than normal, and varied considerably in size. A great majority of fibers measured less than 25 um in diameter. There were occasional fibers less than 5 um in diameter (Fig. 1). The myofibers were generally round and contained characteristic central nuclei in 68% of myofibers. Longitudinal sections often showed chain nuclei (Plate 2)Although one central nucleus was the commonest variety, there were 2 nuclei in 31% and more than 3 in 8% of all the myofibers with central nuclei (Table 1). There were occasional degenerated fibers. Fibrosis was negligible and there was no inflammatory change in the specimen. No enzyme histochemistry was done with this material.

DISCUSSION

Among congenital myopathies myotubular myopathy is the only disease that can be diagnosed histologically without enzyme histochemistry and special staining. It is because of it's characteristic central location of sarcolemmal nuclei in both cross and longitudinal sections. Although there is no further subtypes of myotubular myopathy Engel et al (1968)[2] reported a case of myopathy in a 11 month old boy with a severe and progressive weakness, dying at 11 months of age. In this particular case myofibers showed type I fiber atrophy. Later Bethlem et al (1969)[3] reported further case of this condition and advocated that type of myopathy. In our case Type I fiber atrophy. could not be evaluated because of paraffin embedding of the specimen. There is another form of myotubular myopathy described by van Wijngaarden et al (1969)[4]. It is severe X-linked myotubular myopathy which shows 20% mortality of affected males in the neonatal period. Since our case showed clinically very slowly progressive course and negative family histroy, X-linked myotubular myopathy of Bethlem is not likely diagnosis.

This pateint under discussion had delay in early motor milestones, and the muscle weakness was more marked in shoulder girdle. These findings are rather commonly seen in myotubular myopathy. Although not definite this patient showed slowly progressive nature of disease which occurred despite the improvement of general growth pattern particularly after medication of Oxandrolene. This progressiveness of muscle weakness has been observed in cases of Spiro et al (1966)[5] and Sher et al (1967)[6]. Involvement of extraocular muscle and facial muscle which is sometimes seen in myotubular myopathy was not observed in this case.

On light microscopy myodegenerative changes were not convincing in this case. However, myofibrillar degeneration can be seen ultrastructurally (Dubowitz, 1985)[7]. Loss of plasma membrane component of the sarcolemma was observed by Dub-

owvitz et al (1985)[7] in severe neonatal cases. And together with collections of umusual dense tubules they suggested alteration of T system component. However, the pathogenesis of myotubular myopathy is still unknown. Since the amount of desmin that is highly concentrated is fetal myofibers is not increased in cases of myotubular myopathy (Thornell et al, 1983)[8] and also because of the fact that various ultrastructural changes seen in this disease, it is difficult to say this disease is related to myopathy of arrested myotubular stage of fetal muscle. In this regard "centronuclear myopathy" rather than myotubular myopathy, might be more appropriate term to use as suggested by Sher et al (1967)[6].

REFERENCES

1) Kakulas BA, Adams RD: *Diseases of Muscle, 4th ed. Harper & Row, Publishers, Philadelphia, p 353-358, 1985*
2) Engel WK, Gold GN, Karpati G: *Type I fiber hypotrophy and central nuclei. A rare congenital muscle abnormality with a possible experimental model. Arch Neurol 18:435-444, 1968*
3) Bethlem J, Meijer AEFH, Schellens JPM: *Centronuclear myopathy. European Neurol 1:325, 1968*
4) Van Wijngaarden GK, Fleury P, Bethlem J, Mekjer AEFH: *Familial myotubular myopathy. Neurol 19:901-908, 1969*
5) Spiro AJ, Shy GM, Gonatas NK: *Myotubular myopathy. Arch Neurol 14:1-14, 1966*
6) Sher JH, Rimalovski AB, Athanassiades TJ, Aronson SM: *Familial centronuclear myopathy; a clinical and pathological study. Neurol 17:727-742, 1967*
7) Dubowitz V. Muscle Biopsy: *A practical approach 2nd ed. Bailliere Tindall, London, p 443-459, 1985*
8) Thornell LE, Edstrom L, Eriksson A, et al: *The distribution of intermediate filament protein (skeletin) in normal and diseased human skeletal muscle. J Neurol Sc 47:153, 1980*

＝국문초록＝

근세관성 근병증
(1증례 보고)

서울대학교 의과대학 병리학교실 및
서울대학교병원 소아병리과

지 제 근

5세 남아에서 진단된 선천성 근병증인 근세관성 근병증의 1예를 기술하였다. 본예는 30세 어머니의 첫번째 아들로 태어났으며 성장 발달 장애와 더불어 반복적 폐렴을 앓았으며 특히 운동기능 지둔이 현저하였다.

5세 되든해부터 서울대학교병원 소아과 외래에서 관찰하던중 치료에 반응하지 않으면서 서서히 진행하는 근위약증을 확인하고 근생검을 시행하였다. 환자의 가족력에 특기사항은 없었다.

근생검은 *rectus femoris*에서 하였으며 현미경 검사상 근섬유는 대부분이 작아서 평균 15～20 *um*의 직경을 가졌으며 횡단면에서 특징적으로 중앙으로 편위된 핵을 가진 섬유가 전체근섬유의 약 70%를 차지하였다. 그외에는 특별한 이상소견을 나타내지는 않았다. 본 예는 한국문헌상 근세관성 근병증의 첫번째 기록이라고 생각된다.