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Neuropathology Education

Kyphoscoliosis and easy fatigability in a 14-year-old boy

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CLINICAL COURSE

The patient was a 14-year-old Thai boy who presented at an orthopedic clinic with kyphoscoliosis first detected 1 year prior to medical attention. He was the first child of non-consanguineous parents; the pregnancy and delivery were uneventful. He had normal developmental milestones. The patient noticed easy fatigability after exercise which worsened during the past year. His younger brother was 10 years old and healthy. There was no history of neuromuscular disease in his family. His father passed away due to an unrelated incident. General examination revealed a body weight of 30 kg and a height of 149 cm, bilateral ptosis, high-arched palate, kyphoscoliosis, and asymmetrical chest wall. Proximal muscle weakness of grade 4 by Medical Research Council Scale in all extremities and areflexia were noted. The muscle tone was normal. Serum CK was 49 IU/L. Echocardiogram showed mild pulmonary and tricuspid regurgitation. Pulmonary function tests showed restrictive lung disease; the forced vital capacity was 1.56 L (51% of predicted). Sleep study revealed apnea-hypopnea index 13.6 per hour associated with severe oxygen desaturation (minimum SpO_2 39.0%).

PATHOLOGICAL FINDINGS

Muscle biopsy from the right quadriceps showed varying fiber sizes with type 1 hypotrophy and type 2 hypertrophy. The type 1 fibers were predominant (91%). Cap structures were seen in 32% of all fibers (Fig. 1). Ultrastructurally, the cap structures were composed of disorganized thin myofibrils and thickened Z-lines (Fig. 2). Nemaline rods were not present. Genetic analysis using genomic DNA identified a heterozygous c.415_417delGAG (p.Glu139del) in exon 4 of *TPM2*. The genetic tests were not performed in other family members.

DIAGNOSIS

TPM2-related cap myopathy.

DISCUSSION

Cap myopathy is a rare congenital myopathy characterized by presence of muscle fibers with cap structures on muscle biopsy and prominent respiratory muscle involvement. It is associated with dominant mutations in *TPM2*, *TPM3* and *ACTA1* genes, in descending order.[1,2]

Histologically, in cases with genetic results, cap structures range from 4% to 100% in muscle fibers.[1] Fidzianska reported two neonatal-onset cases with childhood death containing caps in 70–75% of fibers and two other childhood-onset cases with slowly progressive course containing caps in 20–30% of fibers, suggesting association of disease severity and the frequency of cap structure.[3] The number of caps seems to increase as the patients have aged.[4,5]

Onset of cap myopathy ranges from the neonatal period to childhood. Respiratory insufficiency is usually the major problem in patient management. The other common clinical manifestations include neonatal hypotonia, high-arched palate, myopathic facies and scoliosis. Muscle weakness is predominant in proximal muscles, which is non-specific. Serum CK is usually normal or slightly elevated. A case with distinctive abnormal cardiac function[6] and several cases with mild non-specific cardiac abnormalities have been reported.[1] Interestingly, one of the reported cases shows continuous gradual clinical improvement.[5]

Since all three causative genes in cap myopathy are also associated with nemaline myopathy (NM), it is not surprising to have concurrent caps and rods in the same patients[2,7]

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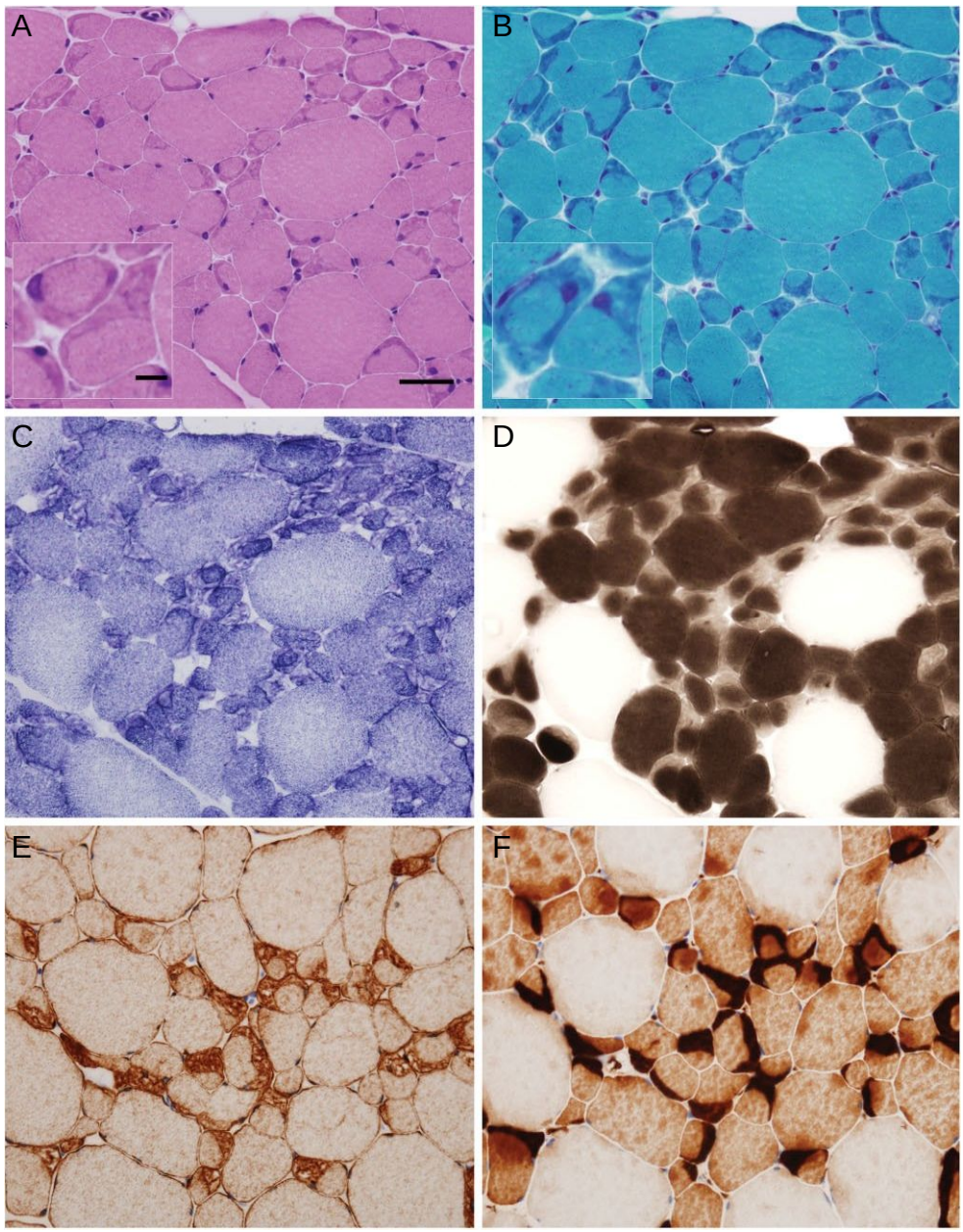

Fig. 1 Cap structures at the periphery of the small fibers in HE stain (A). Caps are highlighted by modified Gomori trichrome stain (B) and nicotinamide adenine dehydrogenase tetrazolium reductase stain (C). The small fibers are type 1 demonstrated by ATPase stain (pH 4.4) and the cap areas are negatively stained (D). The caps are positive for desmin (E) and alpha-actinin (F). Bar = 50 μm, inset bar = 10 μm.

or have a family member with NM[4,8] although cap myopathy is much less common. Muscle biopsy findings of some cap myopathy patients were consistent with congenital fiber type disproportion (CFTD) at a younger age.[5,8] This may represent either a disease spectrum or insufficient tissue sampling since CFTD is also associated with *TPM2* and *TPM3* mutations.[2] Most cap myopathy patients are sporadic yet a few probable autosomal dominant familial cap myopathy cases have been reported.[1,7] It is likely that most cases are affected by *de novo* dominant mutations causing too severe phenotypes to have offspring. Overlapping phenotypes between cap and nemaline myopathies include facial muscle weakness, high-arched palate and respiratory complications. The severity of both myopathies can range from mild to fatal.

The most common recurrent mutation in cap myopathy is p.Glu139del in exon 4 of *TPM2* gene and this mutation seems to be mostly related to cap myopathy, although six patients with different phenotypes have been reported.[2,6,7,9] Most patients with p.Glu139del, including our case, devel-

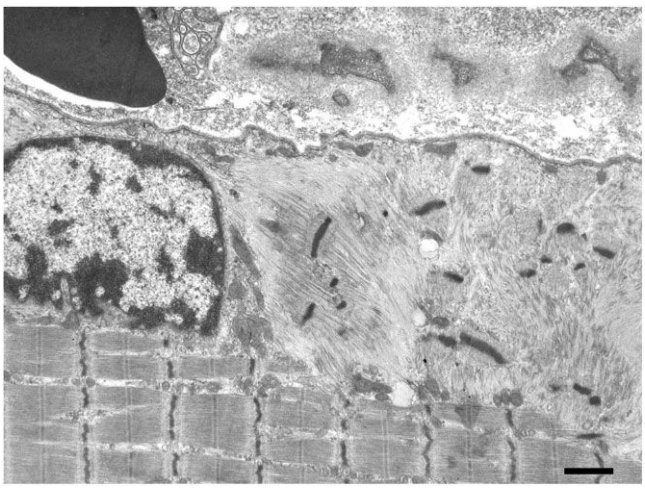

Fig. 2 Electron microscopy study of the cap structures shows disorganized thin myofibrils and thickened Z-lines. Bar = 1 μm.

oped symptoms during childhood, except for one case that presented in the neonatal period.[9] Our patient and two of the reported cases noticed developed scoliosis in a short period of time.[6,7] This feature has not been documented in cap myopathy patients with other mutations. It is possible yet inconclusive that p.Glu139del might affect axial muscles in later stage but progress at a faster rate compared to the other mutations.

In conclusion, we report a case of cap myopathy in a 14-year-old Thai boy. It is the first case reported from Asia and shares a common mutation, p.Glu139del, which was previously identified in patients with European ancestry.[2,6,7,9]

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DISCLOSURES

All authors report no disclosures.

REFERENCES

1. Schreckenbach T, Schroder JM, Voit T *et al*. Novel TPM3 mutation in a family with cap myopathy and review of the literature. *Neuromuscul Disord* 2014; **24**: 117–124.
2. Marttila M, Lehtokari VL, Marston S *et al*. Mutation update and genotype-phenotype correlations of novel and previously described mutations in TPM2 and TPM3 causing congenital myopathies. *Hum Mutat* 2014; **35**: 779–790.
3. Fidzianska A. "Cap disease" – a failure in the correct muscle fibre formation. *J Neurol Sci* 2002; **201**: 27–31.
4. Cuisset JM, Maurage CA, Pellissier JF *et al*. "Cap myopathy": case report of a family. *Neuromuscul Disord* 2006; **16**: 277–281.
5. Ohlsson M, Quijano-Roy S, Darin N *et al*. New morphologic and genetic findings in cap disease associated with beta-tropomyosin (TPM2) mutations. *Neurology* 2008; **71**: 1896–1901.
6. Clarke NF, Domazetovska A, Waddell L, Kornberg A, McLean C, North KN. Cap disease due to mutation of the beta-tropomyosin gene (TPM2). *Neuromuscul Disord* 2009; **19**: 348–351.
7. Tasca G, Fattori F, Ricci E *et al*. Somatic mosaicism in TPM2-related myopathy with nemaline rods and cap structures. *Acta Neuropathol* 2013; **125**: 169–171.
8. Tajsharghi H, Ohlsson M, Lindberg C, Oldfors A. Congenital myopathy with nemaline rods and cap structures caused by a mutation in the beta-tropomyosin gene (TPM2). *Arch Neurol* 2007; **64**: 1334–1338.
9. Lehtokari VL, Ceuterick-de Groote C, de Jonghe P *et al*. Cap disease caused by heterozygous deletion of the beta-tropomyosin gene TPM2. *Neuromuscul Disord* 2007; **17**: 433–442.