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Case Report

A Boy with suspicion of type V glycogen storage disease

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Abstract

Background : Glycogen storage disease subtypes V (GSD-V; McArdle disease; Myophosphorylase deficiency; Muscle glycogen phosphorylase deficiency) is caused by mutation in the gene encoding muscle glycogen phosphorylase. The clinical symptoms usually begin in young adulthood with exercise intolerance and muscle cramps. Transient myoglobinuria due to rhabdomyolysis may occur after exercise and may cause acute renal failure.
Case : A 13 year old boy was referred to Dr.Kariadi Hospital with complaints of swelling all over the body, dark-colored urine, fever, stiffness on the fingers and could not walk anymore. Physical examination showed generalized edema, inferior paraparese, facial nerve paralysis, and spleen enlargement. Brain MRI with contrast showed multiple lesions in caudatus nucleus and bilateral putamen. Histopathology of liver biopsy was metabolic disease that tend to be carbohydrate metabolic disorder.
Discussion : Almost all McArdle disease patients show some kind of exercise intolerance like early fatigability, myalgia, contracture and myoglobinuria induced by exertion. The definitive diagnosis is made by muscle histochemistry and the finding of absent functional muscle phosphorylase. There is no cure for McArdle disease, and as yet no specific treatment can be recommended.
Conclusion : Patient was assessed as suspicion type V glycogen storage disease. Patient got nutritional therapy with vitamin B6, B12 supplementation and physiotherapy. There were some investigations that could not be done during the hospitalization, such as the forearm ischemic exercise, myoglobinuria evaluation, creatinine kinase and gene analysis.

Keywords : Type V GSD, children, metabolic disease

Anak Laki-Laki dengan Kecurigaan *Glycogen Storage Disease* Tipe V

Abstrak

Latar belakang : *Glycogen storage disease* subtipe V (GSD-V; penyakit *McArdle*; defisiensi miofosforilase; defisiensi fosforilase glikogen otot) disebabkan oleh mutasi pada gen fosforilase glikogen otot. Gejala klinis biasanya dimulai pada saat remaja awal dengan intoleransi latihan dan kekakuan otot. Mioglobinuria transien terjadi akibat rhabdomiolisis setelah latihan dan dapat menyebabkan gagal ginjal akut.
Kasus : Seorang anak laki-laki, usia 13 tahun dirujuk ke Rumah Sakit Dr. Kariadi dengan keluhan bengkak seluruh tubuh, urine berwarna hitam, demam, kaku pada jari-jari dan tidak dapat berjalan. Pemeriksaan fisik menunjukkan edema general, paraparese innferior, paralisis nervus fasialis dan pembesaran lien. MRI kepala dengan kontras menunjukkan lesi multipel di nukleus kaudatus dan putamen bilateral. Hasil histopatologi biopsi hepar adalah penyakit metabolik yang cenderung merupakan kelainan metabolism karbohidrat.
Pembahasan : Hampir seluruh pasien dengan penyakit *McArdle* menunjukkan intoleransi latihan, seperti mudah lelah, nyeri otot, kontraktur dan mioglobinuria yang dipicu oleh latihan. Diagnosis definitif adalah berdasarkan pemeriksaan histokimiawi otot dengan tidak ditemukannya enzim fosoforilase otot. Penyakit *McArdle* tidak dapat disembuhkan dan tidak ada terapi khusus yang direkomendasikan.
Simpulan : Pasien didiagnosis dengan kecurigaan *glycogen storage disease tipe V*. Pasien mendapatkan terapi nutrisi suplementasi vitamin B6, vitamin B12 dan fisioterapi. Terdapat beberapa pemeriksaan yang belum dapat dilakukan selama perawatan, yaitu *forearm ischemic exercise*, evaluasi mioglobinuria, kreatinin kinase dan analisis genetika.

Kata kunci : GSD tipe V, anak, penyakit metabolik

INTRODUCTION

Glycogen storage diseases (GSD) are inherited metabolic disorders of glycogen metabolism. Different hormones, including insulin, glucagon, and cortisol regulate the relationship of glycolysis, gluconeogenesis and glycogen synthesis. There are over 12 types. GSD are classified based on the enzyme deficiency and the affected tissue. Disorders of glycogen degradation may affect primarily the liver, the muscle, or both.[1]

Glycogen storage disease subtypes V (GSD-V; McArdle disease; Myophosphorylase deficiency; Muscle glycogen phosphorylase deficiency) is caused by mutation in the gene encoding muscle glycogen phosphorylase, localized to 11q13 by fluorescence *in situ* hybridization. Transient myoglobinuria due to rhabdomyolysis may occur after exercise and may cause acute renal failure. Patients may report progressive muscle weakness, myalgia, and lack of endurance since childhood or adolescence.[1] This case report presents a 13-year old boy with suspicion of type V glycogen storage disease.

CASE PRESENTATION

On June 11th 2015, a 13 year old boy from Demak was referred to Dr. Kariadi Hospital for suspected liver cirrhosis. Ten months prior to the hospital, the parents reported that he had complained swelling all over the body, dark-colored urine, fever, jaundice, nausea, vomiting 4–5 times/day, unconcious temporally if doing sport or ceremony. The patient was admitted to Demak Hospital for two weeks and got improvement. One month prior to hospital admission, the swelling became worse with fever, urine was black especially when the patients got high fever, nausea, vomite 5 times/day, the child was pale, weak, loss of appetite and could not walk anymore. There was stiffness on the fingers, and could not speak clearly. The child was admitted to the Regional General Hospital of Ketileng for one week. The patient then referred to Kariadi Hospital.

The child never had jaundice before, no severe illness, no allergic history, no transfusion history, and no history of routine medication. There was no history of hepatitis or other liver disease among family member. No history of the same disease. The child was in normal developmental status before the admission. He attended junior high school 9th grade. He could follow school lessons and playing with his peers.

Physical examination revealed a 13-year-old boy, body weight: 50 kg, height: 160 cm, general appearance alert, less active, generalized edema. Vital sign was normal, there was no jaundice on both eyes, nasolabial fold was asymmetric, chest examination revealed symmetrical chest expansion, no chest indrawings, normal heart sound, no gallop, breath sound was regular and no crackles. The abdomen was distended with ascites and spleen enlargement (schuffner 4), liver was not palpable, abdominal circumference was 81 cm. Edema on all extremities, physiologic reflexes were decreased and no pathologic reflexes. The inferior limbs was weaker than superior. The examination of genitalia and pubic hair revealed thinning and reddening of scrotal skin, scrotal edema, testicles were about 3,0 cm, pubic hair sparse grow on base of the penis. It was equal to Tanner stage 2.

Laboratory findings showed Hb 9.94 gr/dl, Ht 30%, WBC 6.500/ mm^3, RBC 3.0 million/mm^3, platelets 54.000/mm^3, MCV 100 fl, MCH 33.1 pg, MCHC 33.1 gr/dl, glucose level of 98 mg/dl, ureum 16 mg/dl, creatinine 0.56 mg/dl, calcium 1,8 mmol/L, sodium 136 mmol/L, potassium 3,5 mmol/L , chlorida 104 mmol/L, AST 92 U/L, ALT 42 U/L, alkali phosphatase 505 U/L, gamma GT 32 U/L, total bilirubin 2.2 mg/dl, direct bilirubin 0.83 mg/dl, albumin 1.4 gr/dl, thrombin time 1.6 times, PPT 2.2 times and APPT 2.8 times. Routine urine examination showed urobilinogen 1 mg/dl, blood 250 U/L, erythrocyte 308.5 U/L, bacteri 49.8 U/L. Blood gas analysis: pH 7.36, pO2 26 mmHg, pCO2 189 mmHg, HCO3 14.7 mmol/L, BE -9.2 mmol/L with anion gap 22.2. Prespiration test showed anhidrosis from toe to the 7th thoracal dermatom.

Imaging studies were performed including chest x ray (no cardiomegaly, no infiltrate on both lungs, right pleural efussion), abdomen ultrasonography showed liver cirrhosis, splenomegaly with splenic vein dilatation and ascites. Echocardiography result showed cardiac anatomy and function was normal. Brain MRI with contrast showed multiple lesions in caudatus nucleus and bilateral putamen, with homogen hyperintensity in T2W1, hyperintensity (FLARE) and restricted in DWI that probably neurodegenerative or metabolic lesions DD/ extrapontine myelinolysis. Whole spine MRI with contrast showed no abnormality of vertebral column, there is no lesion in intra and extra spinal cord and annular buldging in 4th – 5th lumbal of intervertebral disc. Liver biopsy result revealed metabolic disease, tend to be carbohydrate metabolic disorder.

The patient was diagnosed with suspicion of type V glycogen storage disease (McArdle disease), paraparese due to neurodegenerative disease, normocytic normochromic anemia, thrombocytopenia, hypoalbumin, prolonged coagulation study. He was given with IVFD of D5 1/2 NS 480/20/5 gtt/minute, ceftriaxone IV 1 gram/12 hour, calcium gluconas IV 10 ml/12 hour, spironolacton 25 mg/8 hour, vitamin B6 1 tablet/24 hour, vitamin B12 1 tablet/24 hour PO. Dietary menu consist of 3 x meals, and 3x 200 ml hepatosol formula, and was programed for transfused with FFP 500 ml. On the twentyfourth day of hospitalization, the child can be discharged and scheduled for routine visits at nutrition metabolic and

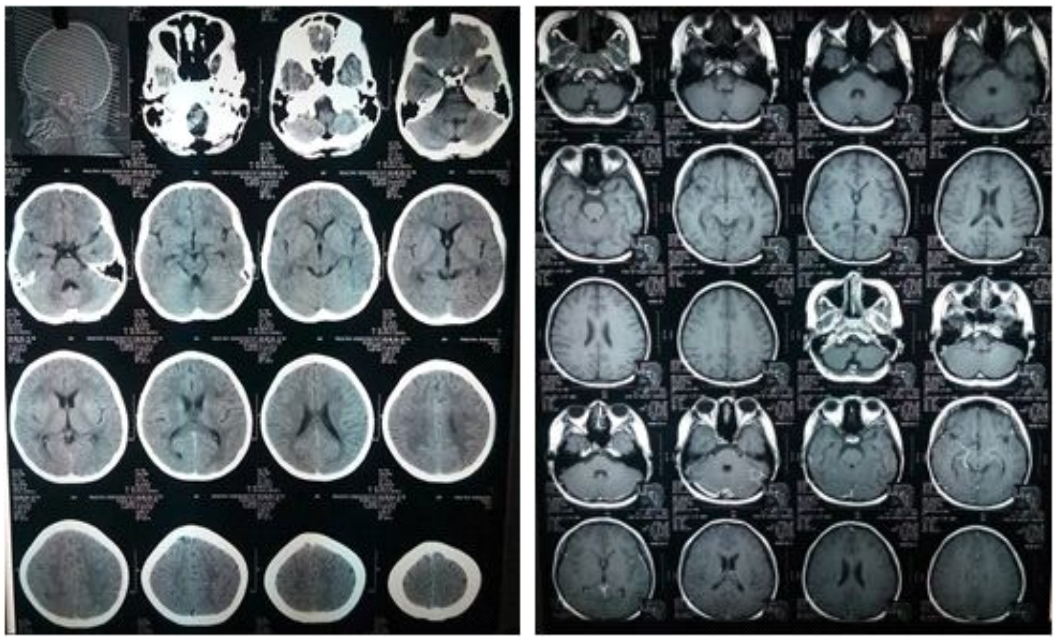

Figure 1. Brain MRI with contrast

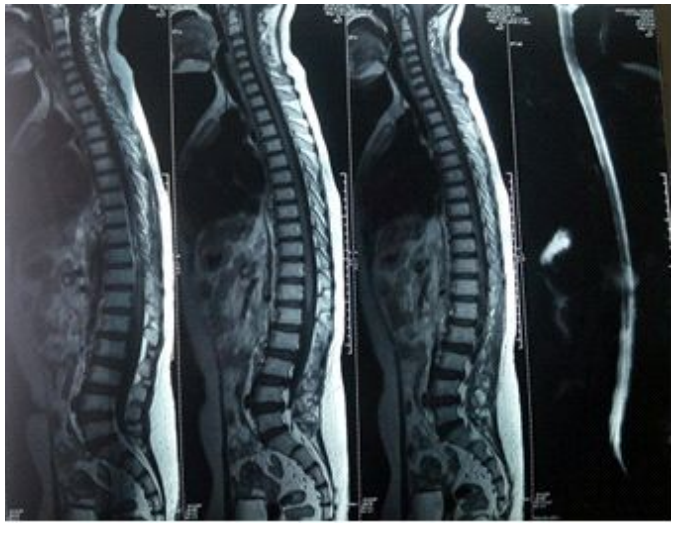

Figure 2. Whole spine MRI with contrast

gastroenterohepatology outpatient clinic.

DISCUSSION

McArdle Disease is a disorder affecting muscle metabolism and is caused by the absence of an enzyme called muscle phosphorylase. This causes an inability to break down glycogen 'fuel' stores. The condition leads to pain and fatigue with strenuous exercise. Sometimes severe muscle damage may develop and occasionally this results in acute reversible kidney failure.[2]

McArdle disease is one of the most frequent genetic myopathies with both sexes equally affected. This disease is inherited in an autosomal recessive manner and produced by pathogenic mutations in both copies of the gene (phosphorylase,glycogen, muscle (PYGM)) encoding the muscle isoform of glycogen phosphorylase and myophosphorylase.[3] The first case was described in 1951 by Brian McArdle. McArdle disease is known as one of the most common disorders of muscle metabolism, with an estimated prevalence of approximately 1 per 100.000 all over the world.[4]

The clinical symptoms of McArdle disease usually begin in young adulthood with exercise intolerance. Almost all McArdle disease patients (96%) show some kind of exercise intolerance like early fatigability,

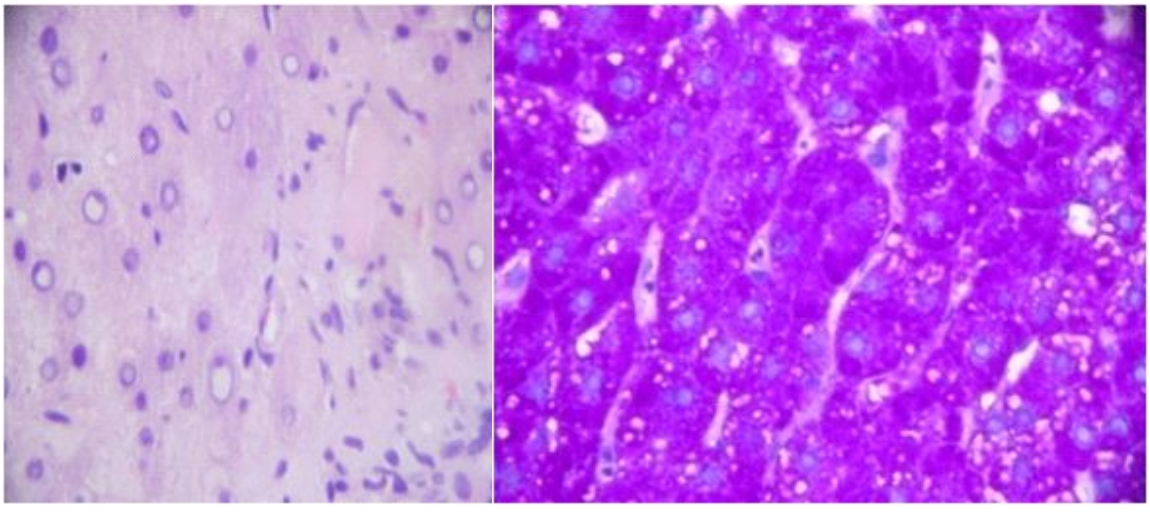

Figure 3. Histopathology of liver biopsy

myalgia, contracture and sometimes myoglobinuria induced by exertion. In addition, the patient usually experience "second wind", which probably results from a switch in the metabolic pathway from the glycolytic pathway to oxidative phosphorylation and is a characteristic feature of this disease. Both exercise intolerance and second wind may be the most important manifestation suggesting McArdle disease in patients with easy fatigability.[5]

Most people present in the second or third decade, although symptoms are often reported retrospectively from childhood.With advancing age, a small proportion of people develop fixed muscle weakness predominantly affecting the shoulder girdle. The main complaints are exercise induced myalgia and fatigue. With severe sustained exercise through pain, a muscle contracture will occur and myoglobinuria (excretion of myoglobin, a muscle protein, in the urine causing dark discolouration), with or without acute renal failure, may follow due to acute rhabdomyolysis (breakdown of the muscles).[6]

Roubertie et al have stressed the heterogeneous spectrum of McArdle disease and have suggested from their findings that the clinical picture can be divided into three types: a neonatal form which is rapidly fatal, a milder form with congenital myopathic features, and a benign classical form with myalgia, cramps, and dark coloured urine. However no correlation has been found between a specific mutation and a phenotype. Also, no factors influencing the clinical features of this syndrome, or for protecting some patients from its manifestations until adult life, have been discovered.[7]

In this case, the patient had exercise intolerance, unconcious temporally if doing sport or ceremony, and dark colored urine. Later on, the patient also suffered stiffness on the fingers, could not walk and speak clearly. Dark colored urine could showed the result of myoglobinuria, but myoglobinuria examination can not be done in the Kariadi Hospital. The patient experienced second wind with a period of less painful and more effective exercise after the initial period of muscle cramps. Based on Roubertie classification, the patient showed a benign classical form with myalgia, cramps, and dark coloured urine. Liver involvement occurred in this patient that marked by the history of jaundice, nausea, vomit and generalized edema.

The genetic defects that result in McArdle disease are autosomal recessive, and heterozygotes are usually asymptomatic. The myophosphorylase gene *(PYGM)* is on chromosome 11q13, and more than 100 mutations have been detected according to the Human Gene Mutation Database. Currently, the p.R50X nonsense mutation (originally known as p.R49X) is the most frequently found mutation among Caucasian patients in North America and Europe. Other mutations are seen in specific ethnic groups; for example, p.F709del/F710del is the predominant mutation in Japanese patients. Almost all of these mutations result in the total absence of functional enzyme and complete disruption of glycogen breakdown in muscle; however, in very rare cases a mild phenotype with minimal residual myophosphorylase activity (1%2.5% of normal) occurs.[4]

McArdle disease patients have low Glycogen Synthase (GS) activity during exercise as well as higher and lower levels of inactive and active enzyme forms, respectively, than healthy controls. The activity of GS is regulated by a complex, multisite phosphorylation mechanism comprising several protein kinases. Furthermore, GS presents a phosphorylation- dependent intracellular distribution with different phosphorylation sites associated with intramyofibrillar and the two other pools of subsarcolemmal and intermyofibrillar glycogen. Depletion of muscle glycogen during exercise activates GS, and this activation is greater when muscle glycogen is lower, resulting in a faster rate of glycogen resynthesis.

The absence of glycogen degradation during exercise in patients with McArdle disease is associated with a slight decrease in GS activity and the link between glycogen and GS may be mediated by protein phosphatase 1, which is targeted to the glycogen molecule. Thus, the high glycogen levels found in the muscle biopsies of these patients could be one of the contributors to GS inactivation, maybe playing a protective mechanism against an exaggerated, harmful accumulation of glycogen.[3,8]

Metabolic myopathies comprise a clinically and etiologically diverse group of disorders caused by defects in cellular energy metabolism, including the breakdown of carbohydrates and fatty acids to generate adenosine triphosphate, predominantly through mitochondrial oxidative phosphorylation. Accordingly, the three main categories of metabolic myopathies are glycogen storage diseases, fatty acid oxidation defects, and mitochondrial disorders due to respiratory chain impairment. Diagnosing these diverse disorders often is challenging because clinical features such as recurrent myoglobinuria and exercise intolerance are common to all three types of metabolic myopathy. Nevertheless, distinct clinical manifestations are important to recognize as they can guide diagnostic testing and lead to the correct diagnosis.[9]

The forearm ischemic exercise (FIE) test is informative but is being abandoned as it is neither reliable, reproducible, nor specific, and is painful. A specific histochemical stain for phosphorylase can be diagnostic except when the muscle specimen is taken too soon after an episode of myoglobinuria.[10,11] The definitive diagnosis is made by muscle histochemistry and the finding of absent functional muscle phosphorylase. Periodic acid Schiff (PAS) staining of the muscle biopsy specimen revealed an increased amount of subsarcolemmal glycogen.[12]

In this case, the forearm ischemic exercise, plasma creatinin kinase activity and DNA analysis can not be evaluated yet. Brain MRI with contrast showed multiple lesions in caudatus nucleus and bilateral putamen, with homogen hyperintensity in T2W1, hyperintensity (FLARE) and restricted in DWI that probably neurodegenerative or metabolic lesions DD/ extrapontine myelinolysis. Histopathology of liver biopsy was metabolic disease that tend to be carbohydrate metabolic disorder. The patient experienced second wind phenomenon, myalgia, weakness, cramps and suspicion of myoglobinuria that supported the diagnosis of McArdle disease as a metabolic myopathy.

There is no specific therapy. Probably, the most important therapy is aerobic exercise, although oral sucrose improved exercise tolerance, and may have a prophylactic effect when taken before planned activity. This effect is explained by the fact that sucrose is rapidly split into glucose and fructose; both bypass the metabolic block in GSD V and hence contribute to glycolysis.[13,14] Potential therapies that have been tried in patients with McArdle disease include manipulation of diet, moderate aerobic exercise, supplementation with creatine and vitamin B6 and gene therapy.[5]

Supplementation of vitamin B6 has been hypothesized to activate the residual phosphorylase activity. Vitamin B6 supplementation seems to be beneficial for exercise intolerance in McArdle disease, although a case-control study will be required to establish the efficacy, appropriate candidates, and optimal dose of vitamin B6. Izumi reported the efficacy of vitamin B6 in patient with McArdle disease. After administration of vitamin B6, fatigability was diminished and ischemic forearm exercise test showed improved glycogenolysis.[5]

Nutritional ketosis has the potential to improve exercise tolerance and ultimately reduce the risk of muscle damage and attendant complications in this patient population. Reason et al reported report the novel experience of three patients with McArdle disease that have adopted a Low-Carbohydrate Ketogenic Diet (LCKD) to manage their exercise intolerance. In each case, a distinct improvement in activity and exercise tolerance was found. Plasma creatine kinase was significantly lowered in all three cases, with two patients exhibiting values within normal range. A carbohydrate restricted diet may provide patients with McArdle disease with a consistent energy substrate for working muscles, thereby reducing the risk of muscle damage and threat of renal failure.[15] In this case, patient got nutritional therapy with vitamin B6 and B12 supplementation. Patient also got physiotherapy during treatment in the hospital.

The most common and potentially serious complication is the breakdown of skeletal muscle tissue. There is no cure for McArdle disease, and as yet no specific treatment can be recommended. McArdle disease itself is not life threatening disease. Patient with this condition are generally in good health, if rhabdomyolisis is avoided. Myoglobinuria can lead to acute renal disease and death. Death can also occur due to respiratory failure in cases of severe muscle weakness. Though not common, but some cases do suffer from seizures. Genetic counseling is recommended for patients who suffer from Mc Ardle disease. McArdle disease is not usually a life-threatening condition, although there are some exceptions.[16]

Quinlivan described a pilot study of neuropsychological performance (brain function) in people with McArdle disease. Ten McArdle patients were compared to ten unaffected people and found to perform significanlly worse on tests. This suggests that the lack of muscle glycogen phosphorylase may also be detrimental to brain function in McArdle people. The brain consumes about 60% of the glucose used by the whole body when resting. The lack of functional muscle glycogen

phosphorylase may affect and reduce brain function in McArdle patient.[17]

In this case, the overall prognosis is dubia ad malam. Reccurent myoglobinuria can lead to acute renal failure and death. Brain involvement occurred in this patient with multiple lesions in caudatus nucleus and bilateral putamen. This abnormalities may affect brain function. Metabolic myopathy disorder caused inferor paraparese and stiffness that can reduce the quality of life.

CONCLUSION

Patient was assessed as suspicion type V glycogen storage disease.. Patient got nutritional therapy with vitamin B6, B12 supplementation and physiotherapy. There were some investigations that could not be done during the hospitalization, such as the forearm ischemic exercise, myoglobinuria evaluation, creatinine kinase and gene analysis.

REFERENCES

1. Ozen H. Gycogen storage disease: new perspectives. *World J Gastroenterol* 2007 ; 13(18) : 2541–2553.
2. Quinlivan R, Martinuzzi A, Schoser B. Pharmacological and nutritiona treatment for McArdle disease (Glycogen Storage Disease type V). *The Cochrane Collaboration* 2010:102–118.
3. Santalla A, Gadea GN, Orteblad N, Brull A, de Luna N et al. McArdle Disease: a unique study model in sports medicine. *Sports Med* 2014;44: 1531–1544.
4. Kitaoka Y. McArdle disease and exercise physiology. Bilogy 2014 ; 3 : 157–166.
5. Di Mauro S. Muscle glycogenoses : an overview. *Acta Myol* 2007; 26 (1) :35–41.
6. Roubertie A, Patte K, Rivier F, Pages A-M, Maire I, Echenne B. McArdle's disease in childhood: report of a new case. *Eur J Paediatr Neurol* 1998;2:269–273.
7. Gordon N. Gycogenosis type V or McArdle's disease. Developmental Medicine and Child Neurology 2013;45:640–644.
8. Bernado A, DiMauro S, Hirano M. A diagnostic algorithm for metabolic myopathies. *Curr Neurol Neurosci Rep* 2010;10(2):118–26
9. Kazemi-Esfarjani P, Skomorowska E, Jensen TD, Haller RG, Vissing A. A nonischemic forearm exercise test for McArdle disease. *Ann Neurol* 2002;52:153–159.
10. Vissing J, Haller RG. A diagnostic cycle test for McArdle's disease. *Ann Neurol* 2003;54:539–542.
11. Salvan AM, Vion-Dury J, Confort-Gouny S, Dano P, Czzone PJ. Increased cerebral glycogen detected by localized 1HMagnetic Resonance Spectroscopy in a patient with suspected McArdle's disease. *Eur Neurol* 1997;37: 251–253.
12. Haller RG. Treatment of McArdle disease. *Arch Neurol* 2000;57:923–924.
13. Vissing J, Haller RG. The effect of oral sucrose on exercise tolerance in patients with McArdle's disease. *N Engl J Med* 2003;349: 2503–2509.
14. Di Mauro S. Muscle glycogenoses: an overview. *Acta Myol* 2007; 26 (1) : 35–41.
15. Skalsky AJ, Dalal PB. Common complications of pediatric neuromuscular disorders. *Psys Med rehabil Clin N Am* 2015;26(1):21–28.
16. Quinlivan R, Buckley J, Twist A, Ball S, Duno M et al. McArdle disease: a clinical review. Journal of Neurology, Neurosurgery and Psychiatry, BMJ Publishing Group 2010;81(11):1182–1188.