Hoffmann's Syndrome associated with Autoimmune Hypothyroidism: a Case Report

Ziynet Uc[1], Suheyla Gorar[2], Gizem Zorlu[3], Seyit Uyar[3]

[1] Department of Endocrinology and Metabolism, Uşak Government Hospital, Uşak, Turkey

[2] Department of Endocrinology and Metabolism, Antalya Training and Research Hospital, Antalya, Turkey

[3] Department of Internal Medicine, Antalya Training and Research Hospital, Antalya, Turkey

Abstract

In this case, we describe a 43 year old female who presented with serious fatigue, progressive muscle weakness and difficulty in walking. Initially, we consider that neurological disorder may be due to her clinical signs and symptoms. Therefore, our investigations were conducted primarily to rule out neurological diseases. But, imaging, electromyography findings and laboratory measurements showed that we faced with Hoffmann's Syndrome relationship hypothyroid myopathy, which rare cause muscular pseudohypertrophy. Clinical and laboratory improvement was observed with thyroxine treatment.

Keywords: Hypothyroid myopathy, autoimmune hypothyroidism, Hoffmann's Syndrome

(Rec.Date: Oct 02, 2015 Accept Date: Nov 12, 2015)

Corresponding Author: Suheylea Gorar, Antalya Training and Research Hospital, Department of Endocrinology and Metabolism Antalya, Turkey
E-mail: sgorar@hotmail.com **Phone:** +90 242 249 44 00, **Fax:** +90 242 249 44 62

Introduction

Myopathy syndromes associated with hypothyroidism are Hoffmann's Syndrome, Kocher-Debre-Semelaigne Syndrome, atrophic form and myasthenic syndrome [1]. Hoffmann's Syndrome which is one of these is a rare disorder in adults, first described by Hoffmann in 1897. It characterizes muscular complaints, pseudohypertrophy and hypothyroidism [2]. Priority clinical manifestations are muscle stiffness, cramps and weakness, myalgia, rhabdomyolysis, atrophic myopathy, pseudomyotonic phenomenon, myasthenic syndrome which unresponsive to endophonium. The most affected muscles are gastrocnemius, deltoid and trapezius [1-3]. Especially, presence of hypothyroidism can give rise to occur several symptoms in clinic such as fatigue, weight gain, cold intolerance, impaired memory, hoarseness, dry skin, muscle aches, tenderness, heart enlargement and myxedema coma [4]. Elevated muscle enzymes and decreased free thyroid hormones levels, electrophysiological study and magnetic resonance imaging (MRI) results and clinical manifestations are helpful to diagnose Hoffmann's Syndrome. Muscle biopsy is not routine recommended for diagnosis. All clinical features of this syndrome respond to thyroid hormone replacement therapy with good prognosis [5-8].

We report a case of a patient who having hypothyroidism, describing serious fatigue and muscle weakness was diagnosed Hoffmann's Syndrome.

Case

A 43 year old woman admitted to our hospital for investigation of serious fatigue, progressive muscle weakness and difficulty in walking. The symptoms had started three months previously with slightly myalgia and muscular stiffness. Also, her complaints had added cold intolerance, forgetfulness, hoarseness of voice and oversleep. She had not known chronic disease or medication in her history.

On physical examination, she had apathic face and hoase voice. Blood pressure, pulse rate and body temperature were 90/60 mmHg, 58 beats/minute and 35.5 °C, respectively. She had macroglossia, her calf muscles were hyperthrophic. Upon neurological examination the patient had proximal and lower limb muscle weakness (4/5), deep tendon reflexes reduced and delayed relaxation. Initially, it was thought as neurologic disorder because of neurological

symptoms and severe muscular weakness of case. It was evaluated neurological system by electromyography (EMG) and MRI. EMG was used for electrophysiological study and result showed low amplitude and short duration motor unit action potentials (MUAPS) with early recruitment suggestive of a myophatic disorder.Cranial MRI was not shown a signs for specific neurologic disease. Muscle MRI of lower limbs was revealed hypertrophy of gluteus medius and maximus on T1 weight. Hyperintensity and myoedema of adductor magnus and longus, biceps femoris, semitendinosus, semimembranosus, gastrocnemius was obtained on T2 weight and short-time inversion recovery (STIR) images.

In cardiologic investigation, echocardiography was normal but electrocardiography showed low QRS voltage with bradycardia. There was not another clinical symptoms, laboratory values and imagine signs for cardiac disease.

Laboratory results showed that distinctly elevated serum levels of triglycerides (TG) 622 mg/dL (50-200 mg/dL) and total cholesterol 250 mg/dL (0-200 mg/dL). Thyroid function testing revealed the serum levels of thyroid stimulating hormone (TSH) > 150 mIU/mL (0.5-5.6 mIU/mL), free triiodothyronine (FT_3) level was 0.24 ng/dL (2.3-4.2 ng/dL) and free thyroxine (FT_4) level was also low 0.20 ng/dL (0.88-1.72 ng/dL). The antithyroglobulin antibody 129 U/mL (normal range: 0-20 U/mL) and antithyroid peroxidase antibody 1128 U/mL (normal range: 0-20 U/mL) levels were highly elevated. The creatinephosphokinase (CPK), one of the muscle enzymes, were markedly elevated and level was 4267 U/L (29-200 U/L), lactate dehydrogenase (LDH) 621 U/L (125-243 U/L), aspartate aminotransferase 140 U/L (5-34 U/L). All other hematological, biochemical, serological and endocrinological hormones such as cortisole, growth hormone, sexual hormones performed and were normal. Thyroid ultrasound signs were compatible with chronic thyroiditis. Although thyroid gland size was normal, thyroid parenchyma commonly had a hypoechogenic-heterogeneous echotexture and surrounding echogenic septations but no thyroid nodules.

Our patient was diagnosed Hoffmann's Syndrome having severe myopathy and autoimmune hypothyroidism symptoms together with laboratory results and imagine features of thyroid ultrasound. Patient was put on oral L-thyroxine replacement therapy at a dose 50 umg/day, increased to 100 umg/ day after one week, and then a week later 150 umg/day. After a month his TSH serum concentration was 3.64 mIU/mL and FT_4 was 1.4 ng/dL. During the therapy

we observed that laboratory values had been seen significantly improvement after one month and the patient's symptoms had entirely disappeared after 3 months. Follow-up MRI showed regression of affected muscles hypertrophy. Table 1 was illustrated laboratory measurements of pretreatment, first week and month of treatment. In addition, physical changes of our case were shown in Picture 1.

Table 1 Laboratory measurements of before treatment, 1st week and month after treatment.

Parameters (normal range)	**Before treatment**	**After treatment 1st week**	**After treatment 1st month**
TSH (0.5-5.6 mIU/mL)	150	89	3.64
FT_3 (2.3-4.2 pg/mL)	0.24	3.1	3.5
FT_4 (0.88-1.72 ng/dL)	0.2	0.69	1.4
TG (50-200 mg/dL)	622	421	191
Cholesterol (0-200 mg/dL)	250	198	158
CPK (29-200 U/L)	4267	1588	278
LDH (125-243 U/L)	621	499	341
AST (5-34 U/L)	140	54	23

TSH: thyroid stimulating hormone; FT_3: free triiodothyronine; FT_4: free thyroxine; TG: Triglycerides; CPK: creatinephosphokinase; LDH: lactate dehydrogenase; AST: aspartate aminotransferase

Picture 1 Physical appearance of pretreatment and after treatment of the case

Discussion

Hypothyroidism is a clinical condition which is caused by a lack of thyroid hormones. It occurs more frequently in women. It usually presents slight or mild clinical symptoms, rarely severe on depending hormones levels. The most signs and symptoms are fatigue, cold intolerance, constipation, weight gain, puffy face, dry skin and hair. In addition, presence of hypothyroid myopathy related to muscular and joint complaints such as aches, stiffness, swelling, tenderness and weakness are worsened physical activity and quality of life. Hoffmann's Syndrome is rare form of hypothyroid myopathy that causes progressive and severe muscular complaints. Regarding to the association and etiology of Hoffman's Syndrome, autoimmune thyroiditis is commonly seen among these patients. Patients have anti-thyroid peroxidase and anti-thyroglobulin antibodies positive in >90% of cases as seen in our case as well. Pathogenesis of hypothyroid myopathy explains the presence of triiodothyronine receptor on the mitochondrial membrane of skeletal muscle. Therefore, direct impact of thyroid hormones on glycolysis and oxidative metabolism in hypothyroidism can cause the structural changes like myofilament loss with accumulation of glycogen, abnormal mitochondria, increased vacuoles, lipids determine in muscle biopsy. Also, muscular hypertrophy can be increased levels of muscle fiber size and number due to accumulation of glycosaminoglycans in Hoffmann's Syndrome [2, 9].

In the literature, the studies show us the prevalence of myopathy in hypo or hyperthyroidism varies between 20% and 80% [6, 8]. In a study performed by Duyff et al., 79% of patients had muscle dysfunction; 54% of them had weakness and 42% of them complained of cramps in

hypothyroidism [6]. One of the clinical signs of polyneuropathy is depressed ankle tendon jerks that were found in 42% of the patients. Short duration motor unit action potentials were seen in 33% of the patients' electromyography in the same study [6]. Cruz et al. showed, in a study with primary hypothyroidism, electrophysiological abnormalities in 87.5% of the patients and 46.6% with myopathic pattern [6]. Upon our patient neurological examination she had proximal muscle weakness, deep tendon reflexes reduced and delayed relaxation. In addition, the appearance of her legs was swollen. Her EMG result showed low amplitude and short duration of MUAPS and muscle MRI of lower limbs revealed hypertrophy of posterior and lateral region muscles.

Serum CPK levels may be elevated in 70%-90% hypothyroid patients [11]. In a study performed by Giampietro et al., serum CPK levels were elevated in 60% of hypothyroid patients [12]. Besides, high levels of CPK in hypothyroid patient are an important laboratory evidence of ongoing Hoffmann's Syndrome. But, CPK serum levels did not correlate with circulating concentration of thyroid hormones and thyrotropine and severity muscle weakness [13]. Our case has apparently high CPK, LDH and AST levels. However, increased levels of CPK, LDH, AST, ALT and aldolase are muscular enzymes in the evaluation of neuromuscular disorders such as myotonic dystrophy, Duchenne or Becker muscular dystrophy. In the case of determining increased levels of these enzymes and clinical findings, muscular disease should not be ignored [1,13]. Because of that radiological test like MRI and electrophysiological study should be performed for differential diagnosis.

Conclusion

Hoffmann's Syndrome is a rare presentation of hypothyroid myopathy. The characteristic features of Hoffman's Syndrome include localized or generalized hypertrophy of muscles in addition to muscle weakness, stiffness, cramps and pain as compared to the classic symptoms of hypothyroidism. Symptoms and physical examination and increased muscle enzymes cause us to suspect about neuromuscular disease. The clinical presentation and biochemical features might make it a bit difficult for the physician to differentiate it from polymyositis or muscle dystrophies. Hoffmann's Syndrome has good prognosis if diagnosed and treated earlier hypothyroidism appropriately. Our case report shows that Hoffmann's Syndrome, though a

rare presentation of hypothyroidism has a good prognosis with timely diagnosis and appropriate management.

References

1. Vasconcellos LF, Peixoto MC, de Oliveira TN, Penque G, Leite AC. Hoffman's syndrome: pseudohypertrophic myopathy as initial manifestation of hypothyroidism. Case report. Arq Neuropsiquiatr. 2003;61(3B):851-4.
2. Nalini A, Gavindaraju C, Kalra P, Kadukar P. Hoffmann's syndrome with unusually long duration: Report on clinical, laboratory and muscle imaging findings in two cases. Ann Indian Acad Neurol. 2014;17(2):217-21.
3. McKeran RO, Slavin G, Ward P, Paul E, Mair WG. Hypothyroid myopathy: A clinical and pathological study. J Pathol. 1980;132(1):35-54.
4. Deepak S, Harikrishnan, Jayakumar B. Hypothyroidism presenting as hoffman's syndrome. J Indian Med Assoc. 2004;102(1):41-2.
5. Ozdag MF, Eroglu E, Ulas UH, Ipekdal I, Odabası Z, Vural O. Early diagnosis and treatment reverse clinical features in Hoffmann's syndrome due to hypothyroid myopathy: a case report. Acta Neurol Belg. 2005;105(4):212-3.
6. Duyff RF, Van den Bosh J, Laman DM, Van loon BJ, Linssen WH. Neuromuscular findings in thyroid disfunction: a prospective clinical and electrodiagnostic study. J Neurol Neurosurg Psychiatry. 2000;68(6):750-5.
7. Mercuri E, Pichiecchio A, Allsop J, Messina S, Pane M, Muntoni F. Muscle MRI in inherited neuromuscular disorders: Past, present, and future. J Magn Reson Imaging. 2007;25(2):433-40.
8. Khaleeli AA, Gohil K, McPhail G, Round JM, Edwards RH. Muscle morphology and metabolism in hypothyroid myopathy: effects of treatment. J Clin Pathol. 1983;36(5):519-26.
9. Simu M, Rosca EC, Reisz D. Thyroid myopathy – a case study. TMJ. 2008;58(1-2):67-9.
10. Cruz MW, Tendrich M, Vaisman M Novis SAP. Electroneuromyography and neuromuscular findings in 16 primary hypothroidism patients. Arq Neuropsiquiatr. 1996;54(1):12-8.
11. Mastropasqua M, Spagna G, Baldini V, Tedesco I, Paggi A. Hoffman's syndrome: Muscle stiffness, pseudohypertrophy and hyperthroidism. Horm Res. 2003;59(2):105-8.
12. Giampietro O, Clerico A, Buzzigoli G, DelChicca MG, Boni C, Carpi A. Detection of hypothyroid myopathy by measurement of various serum muscle markers myoglobin creatine kinase, lactate dehydrogenase and their isoenzymes. Correlations with thyroid hormone levels (free and total) and clinical usefulness. Horm Res. 1984;19(4):232-42.
13. Qureshi W, Hassan G, Khan GQ, Kadri SM, Kak M, Ahmad M, Tak S, Kundal DL, Hussain S, Rather AR, Masoodi I, Sikander S. Hoffmann's syndrome: a case report. Ger Med Sci. 2005;3:Doc05.