American Journal of Medical Case Reports, 2014, Vol. 2, No. 4, 75-77
Available online at http://pubs.sciepub.com/ajmcr/2/4/1

DOI:10.12691/ajmcr-2-4-1

Hoffmann's Syndrome a Presenting Manifestation of Hypothyroidism

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Received April 01, 2014; Revised April 26, 2014; Accepted April 27, 2014

Abstract Hypothyroidism is one of the most prevalent endocrine disorders. Different neuromuscular complications can develop with hypothyroidism. Nonspecific neuromuscular complaints like myalgia, muscle cramps and mild elevation of Creatine Kinase (CK) are the most common myopathic features related to hypothyroidism. Other myopathic features included proximal muscle weakness and myxoedema. The neurological manifestations of hypothyroidism are very unusual to see as initial symptoms and they usually occur late in the course of disease. Muscle hypertrophy is an extremely rare finding in hypothyroid patients. Hypothyroidism presenting as muscle stiffness and muscle pseudo hypertrophy in adults is known as Hoffmann's syndrome. Laboratory investigation in hypothyroid myopathy generally shows increased levels of muscle enzyme. The electrophysiological study may reveal features suggestive of myopathy, neuropathy or mixed pattern. The symptoms and also the serum levels of enzymes return to normal with hormone replacement therapy. We report a case of hypothyroidism with calf muscle hypertrophy and proximal myopathy as the initial symptoms.

Keywords: *hypothyroidism, pseudo hypertrophy, Hoffmann's syndrome*

Cite This Article: Mohammed Nasir Uddin, Abbas Uddin, Mohammed Abbas Uddin Chy, and Taslima Khan, "Hoffmann's Syndrome a Presenting Manifestation of Hypothyroidism." *American Journal of Medical Case Reports*, vol. 2, no. 4 (2014): 75-77. doi: 10.12691/ajmcr-2-4-1.

1. Introduction

The common symptoms of myopathy due to hypothyroidism are proximal muscle weakness, muscle cramps, myoedema on percussion, delay in deep tendon reflexes and rarely development of muscle hypertrophy. [1] Severity of myopathy generally correlates with the duration and the degree of thyroid hormone deficiency. Hoffmann's syndrome is a rare specific form of hypothyroid myopathy, which causes proximal muscle weakness and hypertrophy of muscles. The muscular hypertrophy with muscle stiffness is reported in less than 10% of hypothyroid patients. [2] The hypothyroidism presenting with initial neurological manifestations is very unusual and rare. In children with congenital hypothyroidism, a similar syndrome of muscle hypertrophy (but without cramps) is termed as Kocher-Debre-Semelaigne syndrome. This patient presents with focal or generalized muscle hypertrophy and other systemic features of hypothyroidism (1). There are associated biochemical abnormalities, especially rise of muscle enzymes. However, muscle hypertrophy as first presentation of hypothyroidism is quite rare. There are very few case reports and to our knowledge, this is may be the first report from Bangladesh.

2. Case Presentation

A 30 years old female presented with a history of weakness of all the four limbs for the past four months and difficulty in carrying out his routine daily activities. The weakness is more of proximal muscles than distal, and there was no history of sensory involvement, bowel/bladder disturbance or muscle cramps/stiffness. She also gave history of generalized bodyache, extreme weakness and body swelling. There was no history of cold intolerance, menstrual irregularity. The clinical examination revealed mild peri-orbital puffiness, large tongue, dry coarse skin [Figure 1] b and hoarse voice, non-pitting edema. His pulse rate was 60/minute and blood pressure was 130/80 mmHg. Neurological examination showed normal higher mental functions and cranial nerves. Motor system examination revealed muscle power of 4/5 in all four limbs with predominant proximal muscle weakness, normal muscle tone with generalized hyporeflexia and delayed ankle jerk. There was hypertrophy of calf muscles of both the lower limbs [Figure 2] a and b. Sensory system examination and bowel, bladder functions were normal. The systemic examination was normal.

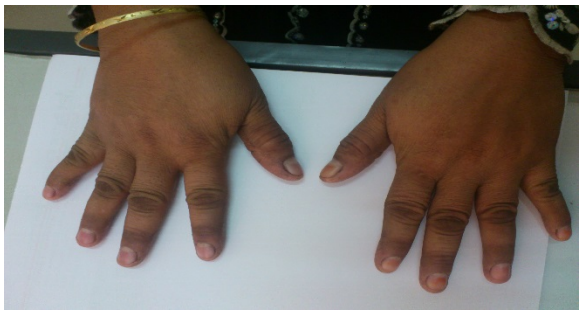

Figure 1. Dry coarse skin

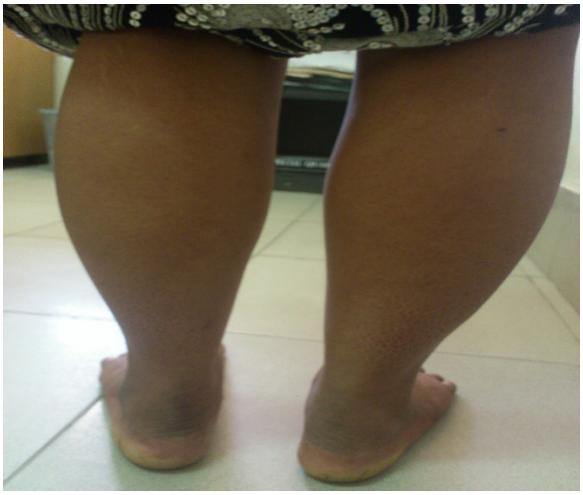

Figure 2. Hypertrophy of calf muscle

Laboratory tests showed, hemoglobin 9.3 gm% with MCV of 100.5 fL. Other cell lines were normal. Serum sodium was 126.7 mEq/L. Liver function test showed SGOT 346 IU/L and SGPT 108 IU/L, but other parameters were normal. Serum cholesterol was 250 mg/dl. Serum creatinine phosphokinase (CPK) was 1685 IU/L (normal<135 IU/L) and Aldolase of 26 IU/L (N <7.6IU/L). Serum Lactate dehydrogenase (LDH) was 1090 IU/L (N <470IU/L). ECG showed low voltage complexes, sinus rhythm and rate 60/minute. Blood test for thyroid function showed, TSH 100 m IU/ml (N: 0.4-5 m IU/ml); FT3 = 30ng/dL (N =58-160 ng/dl); FT4= 1.2 mg/dl (N=4.87-11.72 mg/dl). Anti- microsomal antibody (TPO) was positive 15 IU/ml (N<5.61IU/ml). Anti-microsomal antibody (TPO) was positive 15 IU/ml (N<5.61IU/ml) Ultrasonography of the calf muscles showed increased muscle mass with focal accumulation of connective tissue. Echocardiography showed preserved LV systolic function. Thus the case was finally diagnosed as a case of hypothyroidism presenting with pseudo-hypertophy of muscles as the first presentation, known as Hoffman's syndrome. The patient was put on oral thyroxin replacement and at four months follows up, his calf muscle size was decreased and now her serum creatinine phosphokinase 43 IU/L and TSH 8.05 U/L.

3. Discussion

Hoffmann's Syndrome was first described by Hoffmann in 1897 in an adult who developed muscle stiffness and difficulty in relaxation of muscles after thyroidectomy. [3] The first presentation with myopathy and pseudo hypertrophy of muscles is very rare and unusual to see. Primary hypothyroidism accounts for 95% of the cases of thyroid insufficiency. The main etiology is Hashimoto's thyroiditis, [4] an autoimmune chronic thyroiditis characterized by high levels of thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb). Both TgAb and TPOAb are found in almost 100% of patients with Hashimoto's thyroiditis. [4] The TPOAb is of higher affinity and found in higher concentrations and is the best choice if only a single test is ordered. The etiology of pseudo hypertrophy in Hoffman's syndrome remains obscure and is a matter of discussion. It has been postulated that the mechanisms involved could include an increase in connective tissue, increase in size and the number of muscular fibers. [5,6] There is also change in Type 1 or type 2 fibre atrophy or hypertrophy, myofibril necrosis and regeneration or prominent core-like areas containing amorphous granulo-filamentous material are common pathological findings, which often reverse with treatment. [7] The most common muscles groups involved are the tongue, arm and leg muscles. The muscle hypertrophy and muscle weakness will recede following treatment with thyroid hormones.

Persistently elevated CK is one of the common referral causes to the neuromuscular clinics. Although CK is predominantly reflect muscle related disorders, elevated CK can be seen in non neuromuscular causes as well in non myopathic neuromuscular disorders. Before attributing the high CK to myopathic cause one should rule out non neuromuscular causes that include hypothyroidism, drugs related high CK, toxin, alcohol and trauma. Mild elevation of serum CK also seen in neurogenic muscle atrophy and can be seen with Amylotrophic Lateral Sclerosis (ALS) [1]. Patient with hypothyroidism commonly present with mildly elevated serum CK. Severe elevation of serum CK and rhabdomyolysis with association with hypothyroidism have been [2]. There is no relation between the level of serum CK and the degree of weakness [3,4]. The cause of elevated CK in hypothyroidism is not very well understood. Muscle degerneration is thought to be the cause of elevated CK. Other possible cause includes decrease CK clereance [2]. With L-thyroxine treatment the serum CK return to normal.

Muscle hypertrophy with stiffness as first presentation of hypothyroidism is quite rare [4]. Hoffmann's syndrome is a specific, rare form of hypothyroid myopathy, which causes proximal weakness and pseudo hypertrophy of muscles, due to connective tissue deposition [5]. Usually this is sporadic, though reports of Hoffman syndrome occurring in family members throw light on a genetic basis for the disease [6].

The creatine phosphokinase levels (CPK) will be elevated in thyroid myopathy and very high in some patients (10-100 times greater than the normal level), however, it has no correlation with weakness. [1] The CPK is the best biochemical marker of myopathies. [1] The fall of the enzyme levels with the treatment occurs slowly, varying from weeks, months or even years. The electrophysiological study in hypothyroid myopathy may show findings compatible with neurogenic, myogenic, or a mix of those patterns. The EMG findings compatible with myogenic pattern are diminished duration, and amplitude of motor unit potentials. [8] The voluntary muscle contraction results in early recruitment of short action

motor units, spontaneous fibrillations and complex repetitive discharges. [8] The nerve conduction studies (NCS) may show entrapment neuropathies and axonal sensorimotor polyneuropathy. Our patient presented with predominant proximal muscle weakness and hypertrophy of calf muscles. His CPK levels were elevated 4 times the normal, and TPOAb titers were also elevated. EMG showed myopathic motor unit potentials (MUAPs) with small amplitude in proximal muscles, and nerve conduction study was normal. The patient was started on L-thyroxine (100 µgms once a day) and discharged from hospital. The patient on follow up after 4 months of oral thyroxine showed decreased CPK enzyme levels and improvement in muscle power with mild reduction in muscle bulk.

Calf muscle hypertrophy can have a variety of causes like genetic dystrophies, myositis, Sarcoid infiltration and neurogenic hypertrophy [4,8]. The differentiation between these entities is done by clinical features, serum markers like TSH, EMG studies and response to thyroxin replacement [4]. However, since Hoffman Syndrome can present without other manifestations of hypothyroidism, a high degree of suspicion is needed. A case report by Kaux *et al* showed that Hoffman Syndrome can present in the emergency with severe asthenia and Arthralgia. In them, rapid thyroxin replacement brings quick relief [9].

Hoffman syndrome has quite good prognosis. In some of the reported cases, the symptoms remitted by three months [4,10]. Worsening of symptoms in some at the beginning of treatment may occur, probably caused by rise in metabolic demand induced by thyroxin. In these cases, the concomitant use of steroids during some time of the treatment, as membrane-stabilizing effect can be beneficial [10].

4. Conclusion

Hoffmann's syndrome is very rare condition and its initial presentation with myopathic manifestations can raise diagnostic problems as calf muscle hypertrophy can present in other diseases as well, like Duchenne and Becker's muscular dystrophy, amyloidosis, and focal myositis. Therefore special awareness about this syndrome will lead to the correct diagnosis. The presentation of hypothyroidism may be with polymyositis-like syndrome, serum TSH levels should be routinely tested in all patients with muscle weakness or elevation of CPK. It is also important to emphasize that both the symptoms and serum levels of muscle enzymes return to normal with hormone replacement therapy.

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