

# Hoffman Syndrome; Rare Presentation of Hypothyroidism

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## ABSTRACT

Hypothyroidism may present with various systemic manifestations including hypothyroid myopathy as a recognized feature. It is characterized by muscle weakness, pain, stiffness, and cramps along with elevated muscle enzymes and thyroid stimulating hormone levels. One of the rare presentations of hypothyroidism is Hoffman Syndrome characterized by myopathy along with muscle pseudohypertrophy and raised muscle enzymes. We report a case of Hoffman syndrome that showed significant clinical and biochemical response to thyroid hormone replacement. This case report highlights the clinical features, diagnostic approach and management of Hoffman syndrome. This signifies that early diagnosis and appropriate management improves outcome and prognosis. There have been few such cases reported worldwide and we report this rare case from Pakistan.

**KEY WORDS:** Hypothyroidism. Myopathy. Hoffman Syndrome.

## INTRODUCTION

Thyroid gland plays an important role in growth, development & metabolic functions of body. Classic features of hypothyroidism are weight gain, lethargy, constipation, cold intolerance, depression, myxedema, hoarseness of voice and bradycardia. Patients usually have hair and nail changes, coarsening of facial features and dry skin.<sup>1</sup>

The neuromuscular manifestations of hypothyroidism vary from delayed relaxation of deep tendon jerks to full blown myopathy. Various types of myopathies are seen in association with hypothyroidism. These include the atrophic form, Myasthenic Syndrome, Hoffman Syndrome, Polymyositis-like Syndrome and Kocher-Debre-Semelaigne Syndrome that is described in infants with cretinism.<sup>2</sup> Hoffman Syndrome was described first in 1897 by Hoffman as pseudohypertrophic form of hypothyroid myopathy. Patients with Hoffman Syndrome usually present with muscle weakness, cramps, pain, stiffness, pseudohypertrophy and pseudomyotonic symptoms in contrast to the classic presentations of hypothyroidism as mentioned above.<sup>1</sup> It is rare for patients to present with myopathy as an initial symptom. In view of this rare presentation of hypothyroidism, its diagnosis may be delayed or missed by the clinician. Literature review shows few such cases reported worldwide. We report a case of Hoffman syndrome from Pakistan, along with its clinical features, diagnostic approach and management. This case shows that Hoffman syndrome, being one of the reversible and treatable causes of myopathy, if diagnosed and treated earlier has a good prognosis and decreased morbidity.

## CASE REPORT

A 40 years old male presented in outdoor Medical Department of Sir Syed Trust Hospital, Karachi with 4 years history of gradually progressive weakness, pain, stiffness, cramps and swelling of his legs. After obtaining an informed consent, detailed history was obtained. He had more difficulty in climbing stairs and standing from squatting position. There was no history of numbness in hands or feet. His morbidity gradually worsened with progression of symptoms to his arms and he became dependent even for routine daily activities. He complained of reduced appetite, disturbed sleep, constipation and hair fall as well. There was no history of addiction or drug intake. Family history wasn't significant for such an illness. He was married having a son who was healthy and he had been unemployed since this illness.

His pulse was 58 beats/min (regular rhythm) and blood pressure was 130/80 mmHg with no postural drop. There were no tremors. He had an average built, with coarse facial features and thickened skin (Figure I). He was pale with periorbital puffiness. There was loss of lateral half of eyebrows and dry coarse hair that could be easily plucked off with diffuse alopecia. Hair growth on rest of his body was also reduced with sparse axillary hair. He had pigmentation on lateral aspects of his cheeks and axilla.

His face was asymmetrical, and the asymmetry worsened while smiling. Clinically thyroid wasn't enlarged; there was no lymphadenopathy and no tremors present. Examination of lower limbs revealed normal bulk of thigh muscles, with no fasciculations. However, there was bilateral hypertrophy of calf muscles more on the right side (Figure II). Power was 3/5 at hip; 4/5 at knee, ankle, shoulder, elbow and wrist. Deep

tendon reflexes were diminished including the ankle jerks. Coordination was normal. Examination of his spine revealed no deformity or local tenderness. Rest of his systemic examination and fundoscopy found normal except bilateral non-pitting pedal edema.

Patient was admitted with the provisional diagnosis of Hypothyroid Myopathy/Hoffman syndrome. His initial laboratory evaluation revealed hemoglobin 10.8 g/dL, (MCV 90 fL and HCT 32%) with normal platelets and white cell counts and ESR of 60 mm/hr. Renal functions, electrolytes, serum calcium and urine examination was normal. SGPT was 45 U/L with normal viral markers. Creatinin phosphokinase (CPK) turned out to be 6420 mcg/L (normal 10-120 mcg/L). Lactate dehydrogenase (LDH) was 710IU/L (normal: 140-280 U/L). Thyroid stimulating hormone (TSH) 46.2 mcg/ml (normal: 0.4 - 4.0mIU/L) with free T3 and T4 values 50ng/dl and 0.6ng/dl respectively. Antinuclear Antibody (ANA) profile was negative. Anti-thyroid peroxidase (TPO) antibodies were 73 IU/mL (normal: 35 IU/mL). His ECG showed sinus bradycardia and chest radiograph was normal.

Nerve conduction studies and electromyography show myopathic pattern. Muscle biopsy was reported as fragments of skeletal muscle fibers with variation in size. Decreased endomysial connective tissue with focal fatty and fibro collagenous tissue present.

On the basis of clinical correlation and laboratory evidence patient was started oral thyroxin replacement at an initial dose of 100 µg/day increased to 150 µg/day in 2 weeks. Patient was followed weekly and physiotherapy was started. His thyroid profile and muscle enzymes repeated at 3 monthly intervals showed progressive decline. After 6 months of treatment his power improved to 4/5 in hip and 5/5 in rest of the muscles. His TSH was 4 mcg/mL and CPK was 84 mcg/L. He could walk and climb stairs without support. The edema settled and hair and skin changes partially reversed (Figure 3). Patient was advised to follow regularly and compliance to treatment was ensured.

## DISCUSSION

The neuromuscular symptoms are seen in 30-80% patients of hypothyroidism. Among these delayed relaxation of deep tendon reflexes is the most commonly seen feature (85% of patients).<sup>1</sup> Other manifestations are muscle weakness, stiffness, cramps, wasting, carpal tunnel syndrome, pseudomyotonia and Hoffman Syndrome.<sup>3</sup> The degree of severity and modes of presentation vary widely. However, it is rare for hypothyroid patients to present with isolated neuromuscular complaints without systemic features of hypothyroidism as in this case.<sup>4</sup>

Usually muscle enzymes are raised two to six folds in

hypothyroid myopathy, however in occasional cases they may rise to very high levels. In such cases it might be difficult to differentiate from polymyositis and other types of myopathies.<sup>5</sup> It has been observed that the levels of muscle enzymes usually don't predict the severity of symptoms of myopathy.<sup>6</sup>

Myopathy has a wide set of differentials. Other causes of myopathy to be evaluated in such patients include history of alcoholism, statins, calcium and electrolyte abnormalities, muscle dystrophies, viral infections, paraneoplastic syndromes and the inborn errors of metabolism.<sup>7</sup> Electromyographic studies, nerve conduction studies and muscle biopsy are helpful tools to establish the diagnosis.

Hypothyroid myopathy has a non-inflammatory pathophysiology. The basic mechanisms being explained include an infiltration of the muscles by Myxedema, autoimmune reaction involving the muscles and the membrane dysfunction of muscles.<sup>8</sup>

Electromyographic studies show myopathic pattern and nerve conduction studies may show the neuropathic changes. The muscle biopsy in hypothyroid myopathy shows variation in size of muscle fibers with areas of focal necrosis. There might be an evidence of regeneration. In contrast to Polymyositis, inflammatory infiltrate is occasionally seen in hypothyroid myopathy.<sup>9</sup>

The hypothyroid myopathy responds well to thyroid hormone replacement. The clinical improvement as well as histopathological reversal of changes are achieved with treatment. However, approximately 50% of patients have residual and persistent abnormalities when re-biopsied.<sup>10</sup> The normalization of muscle enzymes may take few weeks to several years and response to treatment varies widely among individual cases.<sup>11</sup> Rhabdomyolysis and respiratory muscle weakness are rare complications that could be life threatening.

It is rare for hypothyroid patients to present with overt myopathy without primary systemic complaints. Hoffman 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.<sup>12</sup> Literature review shows that in contrast to usually seen thyroid myopathy, muscle enzymes may be markedly raised in Hoffman syndrome.<sup>13</sup> The clinical presentation and biochemical features might make it a bit difficult for the physician to differentiate it from polymyositis or muscle dystrophies.

Regarding the association and etiology of Hoffman's syndrome, autoimmune thyroiditis is commonly seen among these patients.<sup>14</sup> Patients have anti-thyroid

peroxidase and anti-thyroglobulin antibodies positive in >90% of cases as seen in our case as well. The genetic transmission hasn't been proved however occasional familial cases have been seen so this possibility can't be ruled out.

Hoffman Syndrome has good prognosis if diagnosed earlier and treated appropriately. Significant improvement in symptoms is seen provided long term compliance to treatment is ensured. Most of the cases improve with thyroid hormone replacement alone. Corticosteroids are not the main stay of treatment. Our patient also improved with thyroid hormone replacement and steroids were not used in this case.

Literature review shows few such cases reported worldwide, particularly in our region. This case report shows that Hoffman syndrome, though a rare presentation of hypothyroidism has a good prognosis with timely diagnosis and appropriate management. As in this case the patient showed gradual but progressive improvement with appropriate management. Thus proving that one can prevent or reduce the morbidity in Hoffman Syndrome by avoiding delay in diagnosis and management.

**Figure I: (Pretreatment) Pale, cold, scaly, dry and wrinkled skin with generalized xerosis Coarse sparse scalp hair, loss of lateral half of the eyebrows (madarosis) and periorbital puffiness is visible**



**Figure II: Calf muscle hypertrophy (More on the right side as compared to left)**



**Figure III: (After 6 months of treatment) Facial puffiness has disappeared Partial reversal of skin and hair changes can be appreciated**



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