Case Report

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Hoffmann syndrome; a rare form of hypothyroid myopathy

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Abstract

Hoffman syndrome is a rare clinical presentation characterized by the presence of proximal weakness and muscle pseudo-hypertrophy in a hypothyroid patient. 50-year-old male presented with gradual onset muscle stiffness and weakness involving both bilateral upper and lower limbs for 3-months duration. Examination revealed generalized hypertrophy of the muscles, mainly involving the Gastrocnemius with proximal muscle weakness and slow relaxing deep tendon reflexes. His Thyroid Stimulating Hormone and creatinine kinase were elevated. Anti-Thyroid peroxidase antibodies were positive. Electromyogram (EMG) and muscle biopsy was suggestive of a myopathic disorder and a diagnosis of Hoffmann syndrome was made. Complete resolution of weakness was observed following thyroxine therapy. Hoffmann syndrome is a rare, myopathic disorder seen in long standing, untreated hypothyroidism and it has a favourable response to thyroid hormone replacement in majority of patients.

Keywords: Hoffmann syndrome, hypothyroid myopathy, hypothyroidism, pseudohypertrophy, myoedema

INTRODUCTION

Hoffman syndrome is a rare clinical presentation characterized by the presence of proximal weakness and muscle pseudo-hypertrophy in a hypothyroid patient. Patients with longstanding, untreated hypothyroidism are more likely to develop symptomatic muscle disease. Rarely hypothyroid myopathy may be the only initial manifestation of hypothyroidism.

CASE PRESENTATION

50-year-old male presented with gradual onset muscle stiffness and weakness involving upper and lower limbs bilaterally for 3-months duration. The weakness progressively worsened, and the patient noticed that he had recent onset difficulty in standing up from squatting position and climbing a flight of stairs. There were no other symptoms such as diplopia, dysphagia or dysarthria. The weakness

was not associated with easy fatigability, diurnal variation or changes with meals. He complained of recent onset hoarseness of his voice and intermittent numbness and pain along the lateral aspect of both hands. He denied of having cold intolerance, constipation, lethargy, loss of appetite, loss of weight or fever. There was no history of recent onset gastroenteritis or respiratory tract infection. He did not smoke or consume alcohol. He was not on medications for any chronic illnesses prior to this presentation.

On examination his Body Mass Index was 30kg/m². He had a generalized dry skin with coarse, lusterless hair with a myxomatous facies (FIGURE 1). His body temperature was 35.7°C. He had peri-orbital oedema and bilateral non-pitting oedema but no obvious goiter or lymphadenopathy noted. His pulse rate was 54 bpm and blood pressure was 85/60 mmHg. Rest of the cardiovascular examination was normal. Neuromuscular examination revealed generalized hypertrophy of the muscles, mainly involving gastrocnemius, deltoids and bicep muscles symmetrically but tenderness, wasting or fasciculation were not present (Figure 2). Muscle power was 4/5 on MRC scale and weakness was more prominent in proximal muscle groups. The ankle jerks were slow relaxing in nature. Myoedema was present. Carpal tunnel syndrome was present bilaterally. There were no signs suggestive of underlying connective tissue disorders. Rest of the clinical examination was normal.

His haemoglobin level was 11.6 mg/dL, serum sodium was 135mmol/L and potassium was 3.7mmol/L. He had elevated creatinine kinase (3990 U/L), creatinine 1.53 mg/dL, TSH 46.9 µIU/mL, reference interval - (0.3-4.2) and reduced free T4 (0.1 ng/dL). He was positive for anti-Thyroid peroxidase antibody (anti-TPO antibody). Ultrasound scan of thyroid gland was suggestive of thyroiditis. Fine needle aspiration and cytology (FNAC) was suggestive of autoimmune thyroiditis. Electromyogram (EMG) of Gastrocnemius and Biceps muscles showed short duration motor unit action potential with reduced amplitude and early recruitment of short action motor units. Nerve conduction studies (NCS) revealed bilateral moderately severe carpal tunnel syndrome. Screening for large fibre peripheral neuropathy was negative. Muscle biopsy was suggestive of hypothyroid myopathy and showed swollen and pale muscle fibres with focal loss of striation (Figure 3). ECG showed sinus bradycardia with small QRS complexes. Troponin I level and 2D echocardiogram were normal. Serum 9 A.M. cortisol level was 713 nmol/L. A diagnosis of Hoffman syndrome was made based on the typical clinical presentation and supportive laboratory evidence. He was started on Thyroxine 50µg and it was titrated gradually up to 150µg daily. His limb weakness gradually improved with treatment over 2-3 weeks with reduction of creatinine kinase and serum creatinine levels. Reversal of myxomatous changes and significant weight loss of 10 kg was observed over 3 months while maintaining euthyroid status.

Timeline

Figure 1: Myxomatous facies

Figure 2: Pseudohypertrophy of left Biceps brachii muscle

Figure 3 A

Figure 3 B

Figure 3: Muscle biopsy of the patient showing myopathic changes; swollen and pale muscle fibres with focal loss of striation (A, B)

DISCUSSION

Hypothyroidism is characterized by deficiency of thyroxine that tends to have a broad spectrum of clinical manifestations. Among many systems involved muscle involvement is noted to be present in 30-80% of the patients diagnosed hypothyroidism, both congenital and adult onset [1]. The manifestations may vary from asymptomatic derangement of creatinine kinase, myalgia, muscle pseudo-hypertrophy, proximal myopathy to rhabdomyolysis and acute compartment syndrome in varying frequencies [2].

Pathogenesis of hypothyroid myopathy is not completely understood and thought to multifactorial in origin. The available evidence suggest that thyroid hormone deficiency leading to impaired glycogenolysis, impaired mitochondrial oxidative metabolism and triglyceride turnover result in selective atrophy of type II fast muscle fibres with compensatory hypertrophy of type I slow muscle fibres [3]. This will result in delayed relaxation of deep tendon reflexes. Accumulation of glycosaminoglycan in muscle fibres leads to pseudo-hypertrophy of muscles [2]. Patients with longstanding, untreated hypothyroidism are more likely to develop symptomatic muscle disease [4]. Rarely hypothyroid myopathy may be the only initial manifestation of hypothyroidism, as seen in our patient[5].

Hoffman syndrome is a rare clinical presentation characterized by the presence of proximal weakness and muscle pseudo-hypertrophy in a hypothyroid patient [5]. Patients usually present with muscle cramps and weakness, pseudo-hypertrophy of muscles, hyporeflexia, delayed deep tendon reflexes and myo-oedema on percussion. The calf muscles are almost always involved whereas the thigh, arm and forearm muscles are involved to a lesser extent [1]. Hoffmann's syndrome was first described by Johann Hoffmann in 1897 in an adult who developed muscle stiffness and difficulty in relaxation of muscles following thyroidectomy. Thereafter similar presentations were reported in patients with Hashimoto's thyroiditis, withdrawal of thyroxine in primary hypothyroidism and in patients undergone post-thyroidectomy irradiation [6].

Mild to moderate rise in serum creatinine kinase is noted in 70-90% of the patients with Hoffmann syndrome [7]. The rise of serum creatinine kinase level does not correlate well with severity of muscle weakness. The Electromyography shows reduced duration and amplitude of motor unit action potential with early recruitment of short action motor units, spontaneous fibrillations and complex repetitive discharges on voluntary muscle contraction [8]. The histopathological changes that are described in Hoffmann syndrome are largely nonspecific and include fibre size variations, type I fibre predominance, type II fibre atrophy, increased number of internal nuclei, disrupted mitochondria, glycogen accumulation, sporadic necrosis and regeneration [9].

Similar clinical presentation of muscle weakness and pseudo-hypertrophy of calf muscles can be also seen in diseases such as Duchenne's and Becker's muscular dystrophy, amyloid myopathy and focal myositis. The importance of differentiating Hoffmann syndrome from above disorders is that it has a favorable prognosis to thyroid hormone replacement.

Thyroid hormone replacement leads to resolution of majority of symptoms and signs related to Hoffmann syndrome. Creatinine kinase level tends to normalize rapidly over few weeks and often precede the resolution of elevation of TSH [10]. The clinical symptoms such as weakness and pseudo-hypertrophy recover more slowly. A subset of patients with Hoffmann syndrome continued to have muscle weakness despite being euthyroid for a mean period of 1 year with a modest overall increase in muscle strength [10]. In such patients, consideration of an underlying myopathic disorder other than Hoffmann syndrome is recommended [9].

CONCLUSION

Hoffmann syndrome is a rare, myopathic disorder seen in long standing, untreated hypothyroidism. In some patients it may be the only initial clinical manifestation related to hypothyroidism. Hoffmann syndrome should be considered as differential in patients who are being evaluated for a possible underlying muscle disorder and

apparent muscle hypertrophy. It has a favorable response to thyroid hormone replacement in majority of patients.

Abbreviations

MRC- medical research council

TSH - thyroid stimulating hormone

T4 – thyroxine

Author declaration

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Author Contributions

All authors were involved in the management of the patient. RR did the initial literature review and wrote the first draft. SP also reviewed literature and corrected the first draft. AG did the final correction before submission. All authors have read and approved the final manuscript

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Availability of data and materials

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Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare that they do not have any competing interests.

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