Hoffmann's syndrome with unusually long duration: Report on clinical, laboratory and muscle imaging findings in two cases

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Abstract

Two adult men presented with the rare Hoffmann's syndrome (HS). Case 1: A 35-year-old male patient had progressive stiffness of lower limbs of 13 years and generalized muscle hypertrophy and myalgia of 3 years duration. Had periorbital edema, dry skin, generalized muscle hypertrophy and spastic dysarthria with hoarseness. Muscle power was normal. Jaw jerk and deep tendon reflexes were exaggerated. Case 2: A 24-year-old male patient presented with muscle hypertrophy from childhood, slowness in motor activities and hearing impairment. For 6 months, he had severe muscle pains, cramps and further increase in hypertrophy. He had yellow tinged, dry skin, hoarseness of voice, gross muscle hypertrophy and minimal weakness. Both had markedly elevated serum creatine kinase (CK) levels and high thyroid stimulating hormone, low free triiodothyronine and free thyroxine levels. Levothyroxine treatment demonstrated remarkable reduction in muscle bulk at 2 months in both and no symptoms at 6 months. Magnetic resonance imaging of lower limbs in both cases revealed almost identical features with involvement of the muscles of posterior and adductor compartment of thighs and posterior and lateral compartments of the legs. Differential diagnosis of long duration muscle pseudohypertrophy and elevated CK levels should include HS.

Key Words

Hoffmann's syndrome, hypothyroidism, myopathy, Pendred syndrome, pseudohypertrophy

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Introduction

Hoffmann's syndrome (HS) is a very rare form of hypothyroid myopathy, first described by Hoffmann in 1897. This syndrome occurs in adults, is characterized by the presence of hypothyroidism with muscle stiffness, pseudohypertrophy, varying degrees of muscle weakness and often painful muscle cramps.[1-4] The gastrocnemius, deltoid and trapezius muscles are generally involved.[4] When this occurs in a cretin child it is known as Kocher-Debre-Semelaigne syndrome.[4] Muscle complaints are due to increased muscle volume secondary to accumulation of myxomatous material and slowness of contraction. Although hypothyroid myopathy represents 5-10% of all acquired myopathies, HS is conspicuously rare.[4,5] Hypothyroidism associated myopathy can be divided into four subtypes: Kocher-Debre -Semelaigne syndrome, HS, atrophic form and myasthenic syndrome.[1,6]

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Magnetic resonance imaging (MRI) is increasingly used for *in vivo* characterization of various inherited and metabolic neuromuscular disorders.[7] It provides a high soft-tissue contrast allowing excellent assessment of striated muscles concerning shape, volume (hypotrophy, hypertrophy) and tissue architecture.[7,8] Due to the lack of ionising radiation, MRI has become a valuable imaging method particularly in muscular dystrophies. We present two men with HS who had an unusually long duration of muscle symptoms. Both cases were documented by clinical examination, blood tests, electromyographic (EMG) studies and muscle MRI.

Case Reports

Case 1

A 35-year-old farmer presented in July 2012 with progressive alteration in the gait of 13 years, slowness in all activities and stiffness of upper limbs of 7 years, progressive dysarthria

with hoarseness of voice, progressive calf hypertrophy and stiffness of lower limbs with proximal muscle weakness and falls for 3 years. Muscle stiffness was present at rest and worsened on walking. He had dryness of skin from childhood, which had worsened over the last 3 years. He had increased sleep and constipation for 3 years. No history of swelling or operation on the thyroid gland, or any medication prior to onset of illness. Examination revealed normal mental functions. Dull look, periorbital and pedal edema, dry skin and brittle nails. Thyroid gland was normal. Neurologically he had generalized muscle hypertrophy including Trapezius and paraspinal muscles [Figure 1] and asymmetrical calf hypertrophy (calf muscle diameter; 34 cm on right, 31 cm on the left). He had coarse facies, hoarseness of voice and mild stiffness of all four limbs. Muscle power was essentially normal except for mild pelvic girdle weakness. Deep tendon reflexes were hyperactive. Ankle jerk although brisk exhibited delayed relaxation. Plantar response was flexor. There was no clinical evidence of peripheral neuropathy. Investigations are depicted in Table 1. Motor and sensory nerve conductions revealed mildly prolonged distal latencies and reduced compound muscle action potentials with mildly reduced conduction velocity suggestive of generalized mild motor sensory demyelinating neuropathy. Electrocardiography (ECG) showed low QRS voltage with bradycardia. 2D echocardiogram was normal. Diagnosis of HS was made. He received levothyroxine replacement at a dose of 1.6 ug/kg/day. At 2 months follow-up, he reported marked improvement in symptoms and reduction in the muscle hypertrophy. By 6 months, he had no muscle symptoms. He was unwilling to undergo repeat investigations.

Case 2

A 24-year-old male patient was evaluated in July 2012 with exertion induced myalgia and progressive generalized muscle hypertrophy of 6 months duration. He reported generalized body aches. Cramps occurred at the peak of muscle aches. He did not have symptoms of myotonia. He apparently had prominent muscles and hoarseness of voice from early childhood along with impaired hearing. Otherwise birth and early developmental history were normal. He had a history of mild dullness for mental activities and slowness since childhood. Interestingly, 3 months prior to visiting our Institution he was referred to a surgical oncologist by a physician with a possible diagnosis of rhabdomyosarcoma of the calves and he underwent a gastrocnemius muscle biopsy which showed non-specific changes. Examination revealed sparse scalp, facial and body hair, yellow tinge on face, dry skin and cold extremities. Voice was hoarse. He had normal mental functions. Facial and bulbar muscles were normal. Thyroid gland was diffusely enlarged. He had severe generalized muscle hypertrophy and huge calves (maximum girth 34 cm) [Figure 2]. Tone was normal. He had minimal difficulty in rising from the floor and muscle power was otherwise normal. Deep tendon reflexes were sluggish. ECG showed low QRS voltage and bradycardia. 2D echocardiogram revealed left ventricular global hypokinesia, reduced left ventricle function, trivial mitral regurgitation (pulmonary artery systolic pressure 34 mm Hg) and moderate pericardial effusion (anterior-1.0 cm, posterior-1.7 cm and lateral-1.4 cm). EMG revealed myopathic process with short duration small polyphasic motor unit potentials. No pseudomyotonic discharges were observed. Nerve conductions were normal. Audiometry revealed bilateral conductive hearing loss, moderately severe on right and mild to moderate on left side. Muscle biopsy was not performed. A diagnosis of HS was considered. Whether the patient also had Pendred syndrome in view of hearing impairment from infancy is a possibility. He received levothyroxine replacement at a dose of 1.6 ug/kg/day and at 2 months follow-up showed remarkable improvement in symptoms and significant reduction in the muscle hypertrophy (left calf diameter of 29 cm and right of 29.5 cm). The thyroid stimulating hormone (TSH) value reduced to 8.29 μ IU/ml. Thyroxine dose was increased and maintained at 100 μg/day. Hearing had improved significantly on follow-up. Repeat serum creatinine was 0.9 mg/dl and creatine kinase was 142 U/L. At 6 months, he had no muscle symptoms [Figure 2c, d and f].

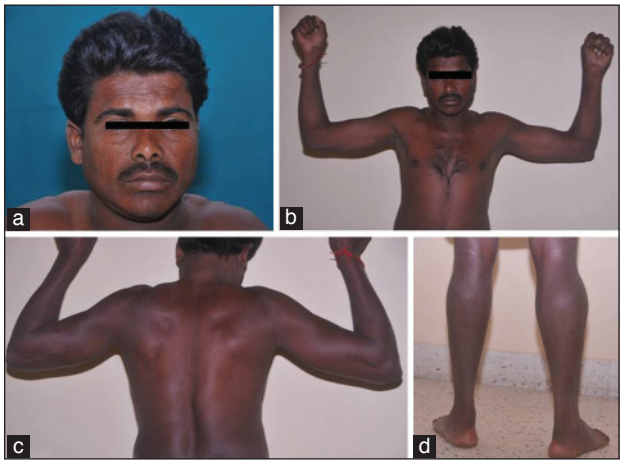

Figure 1: Case 1 — A 35-year-old male patient with periorbital edema and thick dry skin (a); Generalized muscle hypertrophy including Trapezius (b and c); Asymmetrical calf muscle hypertrophy (Right-34 cm, Left-31 cm) (d). No thyromegaly

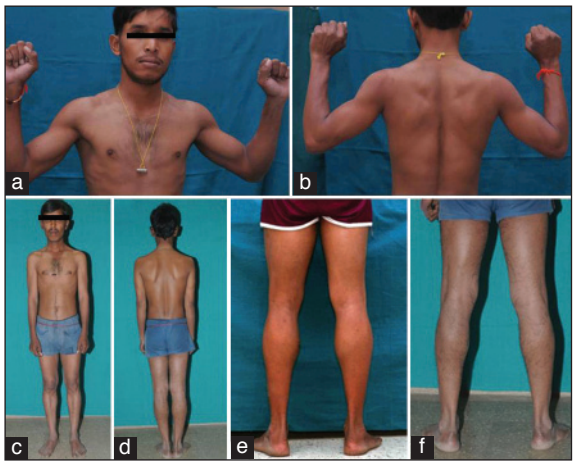

Figure 2: Case 2 — (pre-treatment-a, b and e): A 24-year-old male patient with mild facial puffiness, sparse hair on face, chest and extremities (a and d); Generalized muscle hypertrophy including paraspinal muscles (b-d). Calf hypertrophy (left/right-34 cm). Post-treatment-(c, d and f). At 6 months follow-up. Muscle hypertrophy had significantly reduced; Reduced calf size (left-29 cm; right-29.5 cm). Hair growth had increased

Table 1: Clinical and laboratory findings in both patients

Parameter	Case 1 (M-35 years)	Case 2 (M-24 years)
Pulse	60/min; low volume	60/min; low volume
Blood pressure	124/76 mm Hg	100/80 mm Hg
Hb (g %)	11.4	12.4
TLC	8880	8000
DC-N/L/E/M/B	69/21/03/7/0	64/30/02/04/00
ESR (mm at end of 1 h)	60	42
Platelet count (lakhs/ cu.mm)	2.95	1.67
BUN (mg/dl)	15.4	14.9
Serum creatinine (mg/dl)	1.58	1.71
Serum uric acid (mg/dl)	7.5	–
Serum calcium (mg/dl)	10.08	10.47
Serum phosphorous (mg/dl)	4.95	4.12
Serum total bilirubin (mg/dl)	0.97	0.49
Serum direct bilirubin (mg/dl)	0.25	0.22
Serum total protein (g/dl)	9.2	9.1
Serum albumin (g/dl)	4.9	5.3
A/G ratio	1.1	1.4
AST (U/L)	204	130
ALT (U/L)	77	108
ALP (U/L)	81	79
Serum sodium (mEq/L)	136	138
Serum potassium (mEq/L)	4.24	4.64
Serum chloride (mEq/L)	95.4	99.4
TSH (μIU/ml)	>75	>75
T4 (μg/dl)	<1	<1
T3 (μg/dl)	<40	<40
Creatine kinase (IU/L)	6995	2422
Lactate dehydrogenase (IU/L)	890	760
2D echo with pericardial effusion	No	Yes

Hb = Hemoglobin, TLC = Total leucocyte count, ESR = Erythrocyte sedimentation rate, BUN = Blood urea nitrogen, AST = Aspartate aminotransferase, ALT = Alanine aminotransferase, ALP = Alkaline phosphatase, TSH = Thyroid-stimulating hormone

Special tests such as antithyroid peroxidase antibody or antithyroglobulin levels were not tested in either case due to monetary constraints.

Muscle MRI

Muscle MRI of lower limbs was performed on 1.5-T scanner (Magnetom, Siemens, Erlangen) in both cases at the time of diagnosis and during follow-up in case 2. Sections were obtained from axial planes including a T1-weighted (T1W) spin-echo sequence (repetition time 600-700 ms, echo time 30 ms) and a short-time inversion recovery (STIR) sequence (repetition time 2,500-3,500 ms, echo time 60 ms, inversion time 150 ms), in 10-mm slices. MRI revealed similar findings in both patients with involvement of posterior and adductor compartments of thighs and posterior and lateral compartments of the legs [Figure 3 case 2, Figure 4 case 1]. Axial T1W images revealed hypertrophy of gluteus medius and maximus muscles, adductor magnus, adductor longus, gracilis, biceps femoris, semitendinosus, semimembranosus, soleus, peroneus, gastrocnemius and hyperintensity of the same muscles on T2-weighted (T2W) and STIR images (myoedema) [Figures 3 and 4]. Repeat MRI performed 10 months after treatment in case 2 revealed atrophy of the affected muscles [Figure 3].

Discussion

HS is a very rare form of hypothyroid myopathy in adults that causes proximal weakness and muscle hypertrophy. [4] The most common findings are enlarged muscles, slow movements, delayed deep tendon reflexes, cramps, myoedema and proximal weakness of extremities.[4] Presentation as a persistently isolated myopathy is extremely rare and HS is even rarer.[1-4,9-12]

We report the clinical, biochemical and muscle imaging details of two adult men who presented with classical HS. They had unusually long illness duration. With replacement therapy both patients had a dramatic improvement by 6 months. Case 1 had an illness duration of 13 years and case 2, more than 20 years, while in previous reports the illness duration had ranged from 1 month to maximum of 2 years only.[11,12] Hypothyroid patients may experience myopathy, mononeuropathy or sensorimotor axonal polyneuropathy.[4,13] Case 1 had subclinical electrophysiological evidence of diffuse sensory motor neuropathy. This patient also had features of hyperactive tendon reflexes. Although incidence of myopathy in hypothyroidism is reported to be present in 30-80%,[6,14] complex entities with major symptoms of weakness, muscular cramps and myalgia, along with pseudohypertrophy such as in HS is glaringly rare.

The muscle involvement is reported to be due to conversion of muscle fibers from fast twitch type II to slow twitch type I fibers. The hypertrophy is due to accumulation of glycosaminoglycans (GAG) and gastrocnemius is reported to be almost always involved.[15] Laboratory investigations generally show increased levels of muscle enzymes and low serum thyroid hormones, with elevated TSH as observed in our patients. EMG findings in HS shows myopathic features particularly in gastrocnemius,[11] and this was noted in our cases also.

Systemic symptoms of hypothyroidism were mild in both the patients despite long duration of illness, thus, suggesting a possibility of non-goitrous variant with pseudohypertrophy. This feature has been described in earlier HS.[11] Even in the large series of polymyositis-like syndrome in hypothyroidism, thyromegaly was observed in only 3% of cases.[16] Interestingly, majority of the cases reported with HS and polymyositis like picture predominantly occurred in males as was seen in ours.[17]

Case 2 had presence of moderate pericardial effusion on 2D echocardiography. This feature is described in severe states of hypothyroidism and rarely in Kocher-Debre-Semelaigne syndrome.[18] However, this has not been reported in HS. This patient also had a presence of hearing impairment noted from late infancy. Hence, we considered a possibility of associated Pendred syndrome in this patient. This symptom also improved with Levo-thyroxine treatment.

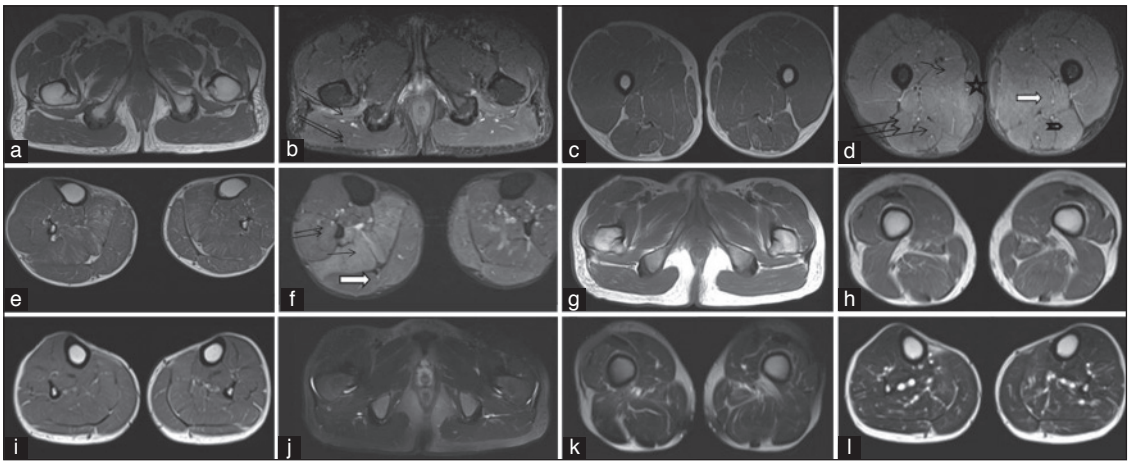

Figure 3: Case 2 — Axial T1-weighted, short-time inversion recovery (STIR) images: (a and b) Hypertrophy of gluteus medius (arrow) and maximus (double arrow); (c and d) hypertrophy of adductor magnus (open arrow), adductor longus (curved arrow), gracilis (star), biceps femoris (double arrow), semimembranosus (arrow), semitendinosus (arrow head); (e and f) hypertrophy of soleus (small arrow), peroneus (double arrow) and gastrocnemius (open arrow). All affected muscles show hyperintensity on T2-weighted and STIR images. Follow-up magnetic resonance imaging (g-l) shows atrophy of previously affected muscles

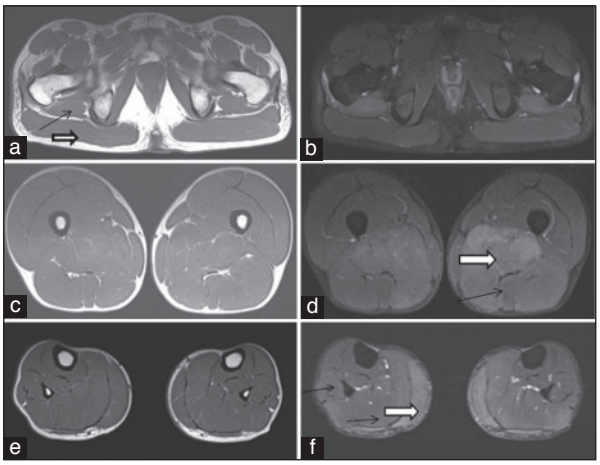

Figure 4: Case 1 — Axial T1-weighted and short-time inversion recovery (STIR): (a and b) Hypertrophy of gluteus medius (small arrow), maximus (open arrow); (c and d) hypertrophy of muscles of posterior and adductor compartment (small arrow) (open arrow); (e and f) hypertrophy of soleus (small arrow) peroneus (double arrow) and gastrocnemius (open arrow). All affected muscles show hyperintensity on T2-weighted and STIR images

MRI study showed predominant affection of postero-lateral muscles of thighs and legs that appeared enlarged on T1W images and hyperintense on T2W and STIR sequences. The deposition of GAG in muscles has been described in HS, but the imaging finding contributing to the same could only be speculative.[1-3] Methods to image GAG are mostly limited to descriptions in joints. Procedures such as delayed gadolinium-enhanced MRI of cartilage and fluid-suppressed sodium inversion recovery are not very specific and even require hardware modification as in the latter method. Recently described method of chemical exchange saturation transfer technique provides *in vivo* visualization of GAG which is not limited to joint.[18] Hyperintensity on T2 and STIR could represent the element of edema associated with myositis as suggested by clinical, EMG and biochemical examination. These two cases with almost identical pattern of muscle involvement suggests a certain pattern of muscle affection in HS. Muscle MRI may be helpful in identifying or differentiating hypothyroid myopathy from muscular dystrophy when there is an overlap or inconclusive findings from other diagnostic investigations.

Clinical suspicion and adequate work-up helps to diagnose and effectively manage this rare and potentially treatable disorder. Treatment is levothyroxine supplement leads to remarkable results and subsidence of muscle hypertrophy in most of the cases[5,11,12,17] and the same was noted in our cases too. It was interesting to note that the hypertrophied, edematous muscles reduced in size and rather showed atrophy. Although the illness duration was unusually long, at 6 months follow-up they had improved completely with normalization of muscle size.

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